

## III.2 Palladium-Catalyzed Carbon–Carbon Cross-Coupling

### III.2.1 Overview of the Negishi Protocol with Zn, Al, Zr, and Related Metals

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#### A. HISTORY AND SCOPE OF THE NEGISHI PROTOCOL

The Negishi coupling (or reaction or protocol) may loosely be defined as the Pd- or Ni-catalyzed cross-coupling through the use of organometals containing metals of intermediate electronegativity, such as Zn (1.6), Al (1.5), and Zr (1.4), the numbers in parentheses being the Pauling electronegativity values.<sup>[1]</sup> Additionally, the use of cocatalysts containing metal salts, most notably Zn salts (e.g., ZnCl<sub>2</sub> and ZnBr<sub>2</sub>),<sup>[2]</sup> has also been included in this protocol. The selection of these metals stemmed from the following observations in a broad-range systematic investigation made mostly in the 1970s.<sup>[3],[4]</sup>

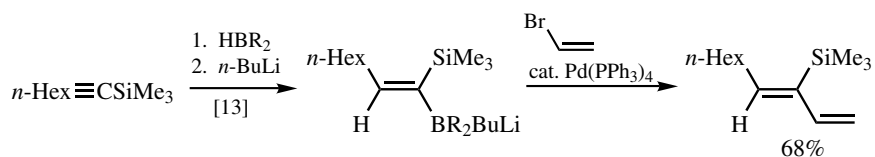
1. Metals of intermediate electronegativities exhibited, in general, the highest catalytic activities in Pd-catalyzed cross-coupling,<sup>[3]</sup> as observed first in alkynyl–aryl coupling reaction (**Table 1** in **Sect. III.1**).

2. The use of Al and Zr permits not only generation of certain stereo- and regiodefined alkenylmetals and the corresponding halides via hydrometallation and carbometallation but also *in situ* cross-coupling under the influence of Pd or Ni catalysts.<sup>[2],[3],[5]–[16]</sup> A series of papers cited above established, for the first time, the hydrometallation–cross-coupling and carbometallation–cross-coupling tandem processes (**Scheme 1**). On the other hand, the corresponding alkenylboron compounds generally exhibited either a very low or no reactivity under similar reaction conditions,<sup>[5],[6]</sup> even though alkynylborates<sup>[3]</sup> and  $\alpha$ -silylalkenylborates<sup>[13]</sup> did participate satisfactorily in Pd-catalyzed cross-coupling (**Scheme 2**). This limitation associated with B has since been overcome by the Suzuki protocol (**Sect. III.2.2**).

3. In cases where the Pd- or Ni-catalyzed cross-coupling reactions of alkenylaluminum and alkenylzirconium derivatives are sluggish, addition of Zn salts (e.g., ZnCl<sub>2</sub> and ZnBr<sub>2</sub>) has significantly accelerated these reactions in many cases (double metal



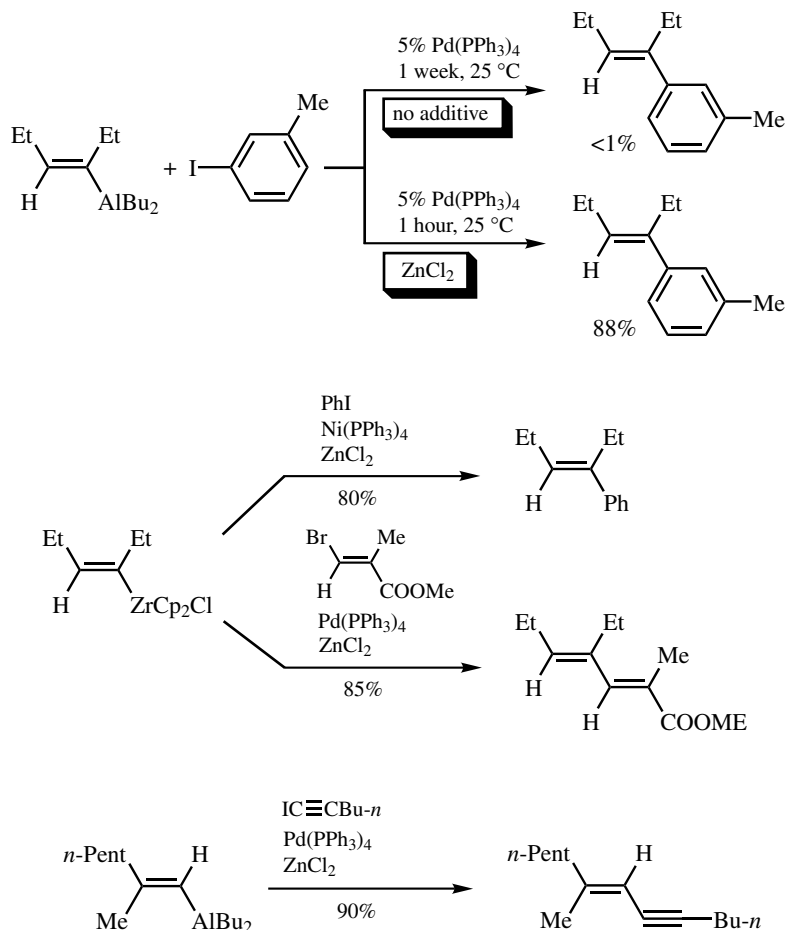
### Scheme 1



Scheme 2

catalysis)<sup>[2]</sup> (**Scheme 3**). Similar beneficial effects of Zn salts have also been observed in the Pd-catalyzed cross-coupling reactions of alkenylcoppers.<sup>[17]</sup>

4. Organometals containing more electropositive metals (e.g., Li and Mg) are generally most reactive in many different kinds of reactions. And yet, the catalytic reactivity of these metals, especially Li, in the Pd-catalyzed reaction is lower than that of Zn in many cases. Because of their high intrinsic reactivity toward many functional groups, they are not very chemoselective in a traditional sense. As a consequence of these two generally



Scheme 3

observable factors, alkali metals and Mg have been less frequently used in Pd-catalyzed cross-coupling. In fact, organolithiums have rarely been used, although some successful examples are known.<sup>[18]</sup> It should be clearly noted that their reactivity under the stoichiometric Pd-promoted coupling conditions is at least as high as or most probably higher than that of Zn.<sup>[18]–[21]</sup> Although still not very clear, it is not unreasonable to speculate that their intrinsically high reactivity itself is hindering the desirable catalytic process through some unwanted side reactions with coordinatively unsaturated organopalladium intermediates.<sup>[20]</sup> Further clarification of this aspect of Pd-catalyzed cross-coupling is highly desirable.

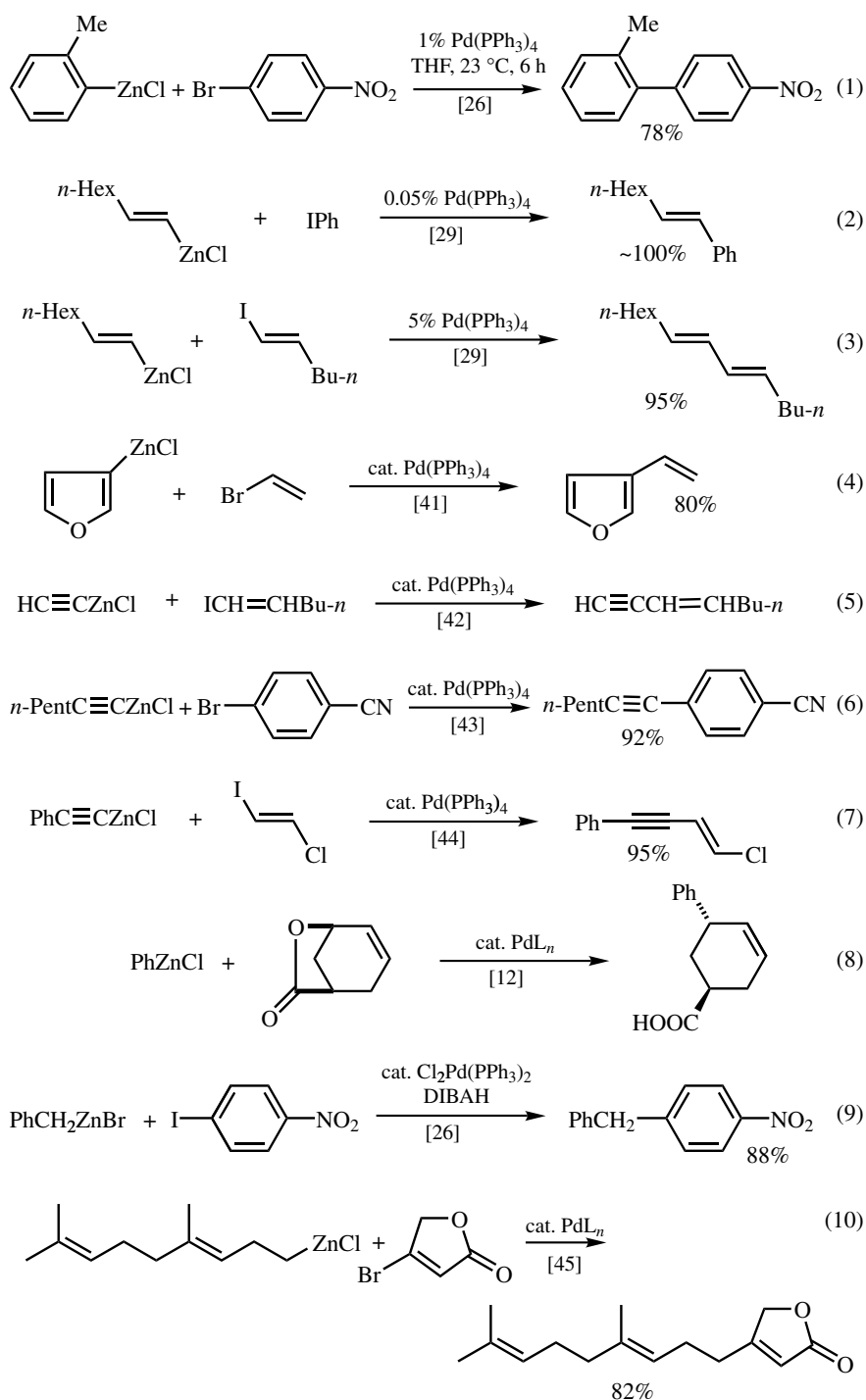
Despite the severe limitations mentioned above, their ability to participate in Pd-catalyzed cross-coupling must not be underestimated in view of (i) their intrinsically high reactivity and (ii) the fact that organometals containing other metals (e.g., Zn, B, and Sn) are often prepared via organolithiums and Grignard reagents. In cases where organolithiums or Grignard reagents are used as the precursors to other organometals, the use of the latter reagents should be experimentally justified. If the former reagents prove to be as satisfactory as the latter, the former reagents should be directly used.

Although the Ni-catalyzed reaction of Grignard reagents has often been called the Kumada coupling or Kumada–Corriu reaction,<sup>[22]–[24]</sup> no name appears to have been associated with the Pd-catalyzed reaction of Grignard reagents and organolithiums, perhaps because they are less frequently used. Some have referred to them as the Kharasch reaction,<sup>[25]</sup> which may include any Grignard coupling reactions catalyzed by transition metal salts. However, the notion of using transition metal–phosphine and other related complexes for achieving highly cross-selective coupling appears to have been lacking in the Kharasch reaction. It seems reasonable to call the Pd-catalyzed reactions of Grignard and organolithium reagents the Murahashi protocol (coupling or reaction) in recognition of his pioneering investigations,<sup>[18],[19]</sup> even though extensive studies by others, most notably Negishi and co-workers,<sup>[26]–[31]</sup> Linstrumelle and co-workers,<sup>[32]–[35]</sup> and Hayashi and co-workers<sup>[36]–[40]</sup> since the late 1970s should also be duly recognized.

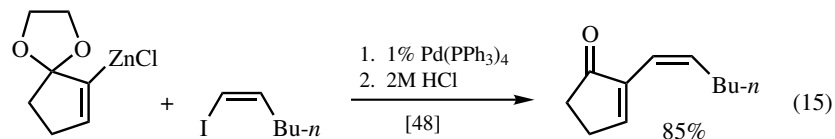
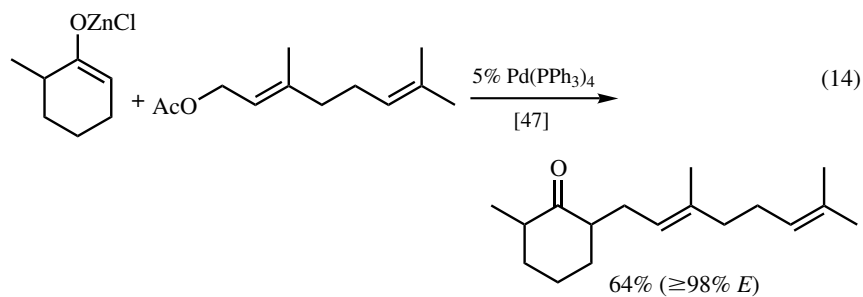
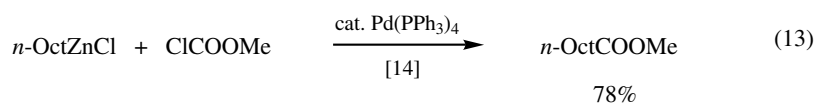
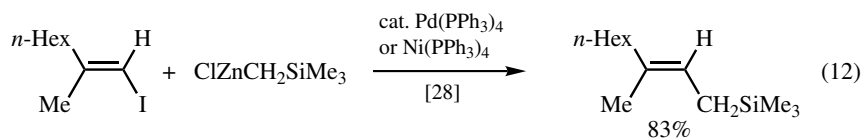
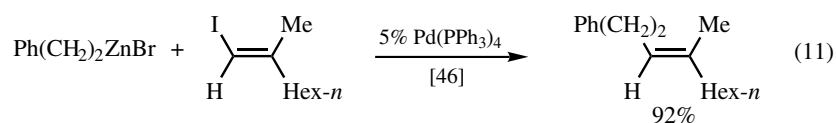
In addition to the prototypical results observed with Al and Zr, in conjunction with Zn salts in some cases, that are shown in **Schemes 1** and **3**, some prototypical results observed with organozincs shown in **Scheme 4** indicate the synthetic versatility of zinc-based Pd- or Ni-catalyzed cross-coupling.<sup>[3],[4],[49]–[52]</sup>

In general, several metals including Zn, B, Al, Sn, Cu, Zr, and even Mg as well as Si are satisfactory in many less demanding cases. In more demanding cases, however, differences in various respects among these metals become more apparent. Although the final selection of the optimal metal counteraction depends on a number of factors as discussed later, Zn has repeatedly been shown to be the most reactive counteraction in Pd-catalyzed cross-coupling. Following the initial systematic counteraction screening<sup>[3]</sup> (**Table 1** in **Sect. III.1**), additional comparative studies to compare the relative merits and demerits of various metal counteractions have been made. As has repeatedly been demonstrated, the superior catalytic reactivity of Zn appears to be clear and observable in many different cases of Pd-catalyzed cross-coupling.

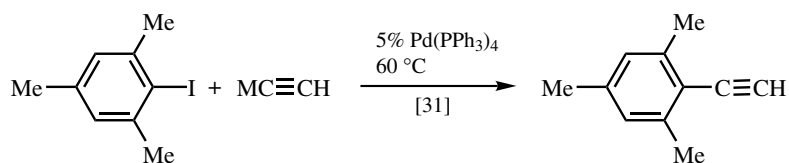
Even in the alkynyl–aryl coupling where Zn, B, Sn, and Mg have been shown to be comparably satisfactory in less demanding cases,<sup>[3],[30],[31]</sup> some clear-cut differences have been shown in more demanding cases<sup>[30],[31]</sup> (**Scheme 5**). This aspect is further discussed in **Sect. III.2.8.2**. Curiously, ethynylborates do not give the desired products in any detectable amount,<sup>[31]</sup> even though higher alkynylborates react satisfactorily.<sup>[3]</sup>



Scheme 4



Scheme 4 (Continued)



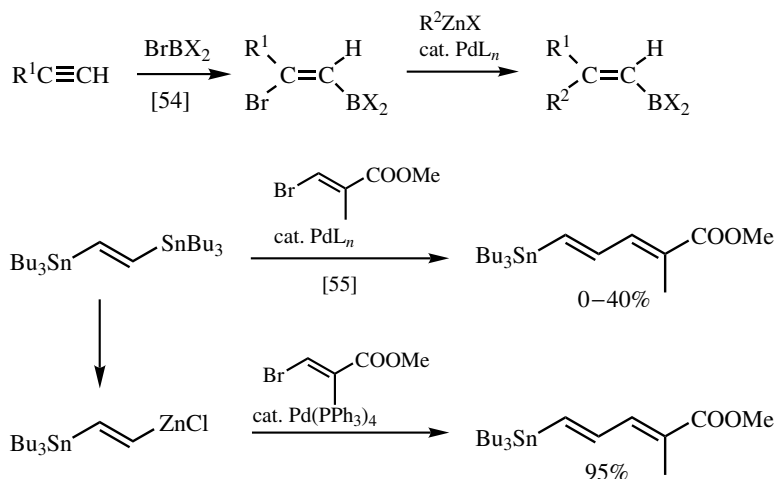
M	Solvent	Time(h)	ArC $\equiv$ CH (%)	ArC $\equiv$ CAr (%)	ARI (%)
MgBr	DMF	48	28	12	66
MgBr	THF-DMF	24	trace	trace	95
ZnBr	THF-DMF	18	74	10	—
SnBu <sub>3</sub>	THF-DMF	24	3	trace	95
SnBu <sub>3</sub>	THF-DMF	72	36	8	52

Scheme 5

The very fact that the Pd-catalyzed reactions of alkenylmetals containing Al,<sup>[2]</sup> Zr,<sup>[2]</sup> and Cu<sup>[17]</sup> can be significantly accelerated with ZnCl<sub>2</sub> or ZnBr<sub>2</sub> (**Scheme 3**) coupled with observations that the corresponding reactions of alkenylzincs proceed at least as fast as the Zn–Pd-cocatalyzed reactions is a clear indication of the higher reactivity of Zn relative to Al, Zr, or Cu. This, of course, does not negate the usefulness of Al, Zr, or Cu; it is nonetheless potentially profitable and important to know their relative catalytic activities.

Objective comparison of the three most widely used metals—Zn, B, and Sn—in aryl- and alkenylmetal reagents is still relatively rare. In many cases, satisfactory results have been obtained with all three metals, and their relative merits and demerits depend on a number of factors. Even in such cases, however, the higher reactivity of Zn is clearly seen in general. For example, in many less demanding cases, the organozinc reactions are run in THF at room temperature with Pd(PPh<sub>3</sub>)<sub>4</sub> or Cl<sub>2</sub>Pd(PPh<sub>3</sub>)<sub>2</sub> as a catalyst. On the other hand, a set of more rigorous and carefully optimized conditions including higher temperatures, more expensive catalysts [e.g., Cl<sub>2</sub>Pd(TFP)<sub>2</sub>, Cl<sub>2</sub>Pd(dppf), and Cl<sub>2</sub>Pd(AsPh<sub>3</sub>)<sub>2</sub>], more expensive solvents (e.g., DMF and NMP), and added reagents (e.g., NaOMe and K<sub>3</sub>PO<sub>4</sub>) are usually necessary to observe comparable results with B (**Sect. III.2.2**) and Sn (**Sect. III.2.3**).

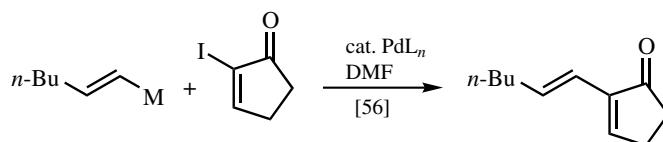
More significantly, organozincs have been shown to be distinctly superior to those containing the other metals including B and Sn in more highly demanding cases, even though the ability of B to elevate its catalytic reactivity with the aid of certain bases (e.g., NaOH and NaOMe) should be clearly noted.<sup>[53]</sup> The fact that  $\beta$ -bromoalkenylboranes obtainable by bromoboration of alkynes react with organozincs as alkenyl bromides without the complication due to their oligomerization and polymerization<sup>[54]</sup> clearly indicates that alkenylzincs are intrinsically more reactive than alkenylboranes (**Scheme 6**). The higher reactivity of alkenylzincs relative to alkenyltins has repeatedly been reported. For example, whereas the Pd-catalyzed reaction of methyl (*E*)- $\beta$ -bromomethacrylate with (*E*)-Bu<sub>3</sub>SnCH=CHSnBu<sub>3</sub> is sluggish, producing the desired coupling product in 0–40% yields under various conditions, the corresponding reaction with (*E*)-Bu<sub>3</sub>SnCH=CHZnCl leads to a 95% yield of the desired product by the preferential reaction of the C–Zn bond in the presence of the C–Zn bond<sup>[55]</sup> (**Scheme 6**). Additional examples indicating the



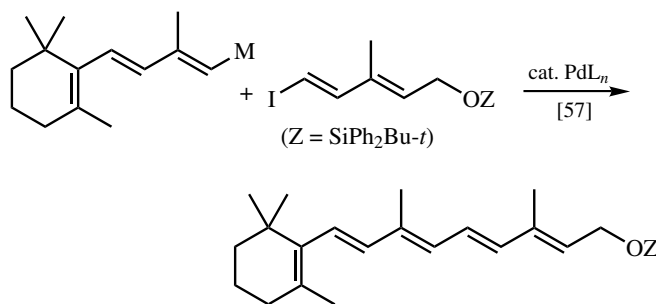
Scheme 6

superior reactivity of Zn relative to B and Sn through comparative studies are shown in **Scheme 7**.<sup>[56]–[62]</sup>

Benzylzinc derivatives not only exhibit a high catalytic reactivity but also are readily formed by direct zincation of benzyl bromides.<sup>[10],[26]</sup> Although allylzinc and propargyl (or allenyl)zinc derivatives can also be prepared similarly, their Pd-catalyzed cross-coupling has not been favorable, as discussed later. Other more usual alkylzinc derivatives<sup>[14],[27],[28],[36],[45]</sup> generally are among the most reactive alkylmetals along with some alkylmagnesium derivatives (**Sect. III.2.11**). The applicability of alkyltins appears to be very much limited. Aside from those metals mentioned above, the synthetic usefulness of alkylboron derivatives should be clearly noted. Alkylboranes can readily be generated via hydroboration of alkenes. Under the Suzuki reaction conditions using certain bases, they have also exhibited a high reactivity leading to favorable results,<sup>[54]</sup> as discussed in **Sects. III.2.3** and **III.2.11**.



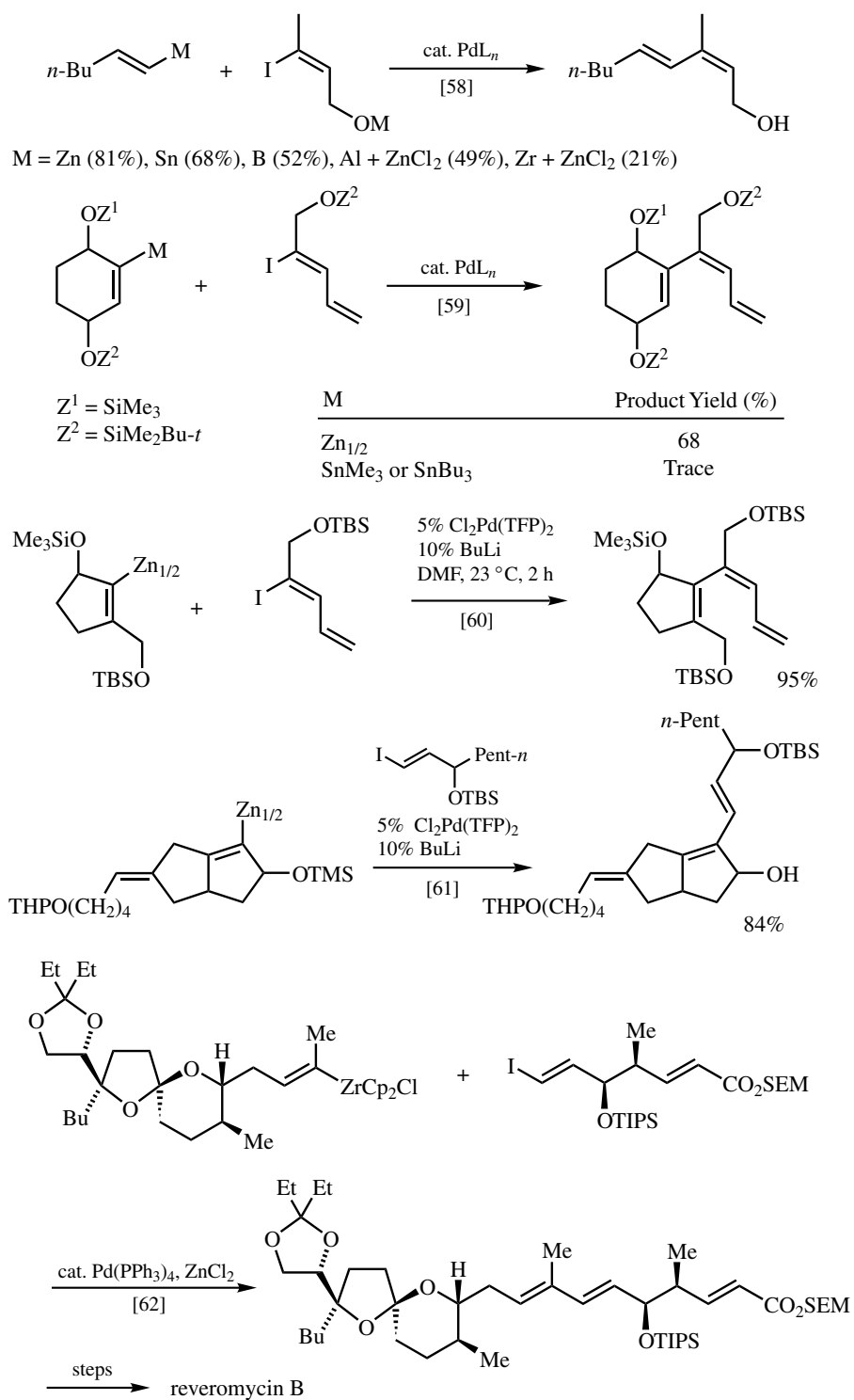
M	Temperature (°C)	Time (h)	Product	Yield (%)
Zn <sub>1/2</sub>	25	1		100
Al(Bu- <i>i</i> ) <sub>2</sub>	25	1		89
ZrCp <sub>2</sub> Cl	25	1		27
SnBu <sub>3</sub>	25	1		Trace
SnBu <sub>3</sub>	60–65	13		64



M	Solvent	Temperature (°C)	Time (h)	Product	Yield (%)
Zn <sub>1/2</sub> THF	25	1	87		
AlMe <sub>2</sub>	THF	25	3		41
AlMe <sub>2</sub> (+ZnCl <sub>2</sub> )	THF-DMSO	25	3		60
Mg <sub>1/2</sub>	THF	25	3		57
SnMe <sub>3</sub>	THF or HMPA	25	3		Trace
SnMe <sub>3</sub>	HMPA	65	3		39
CuMgX <sub>2</sub>	THF	–20 to 25	3		11

**Scheme 7**

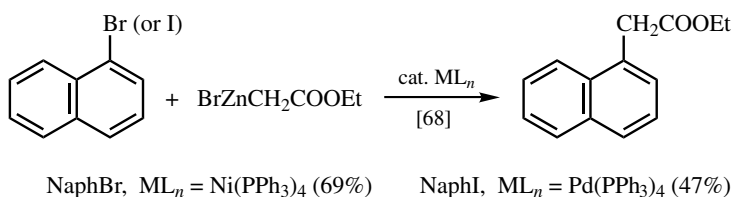
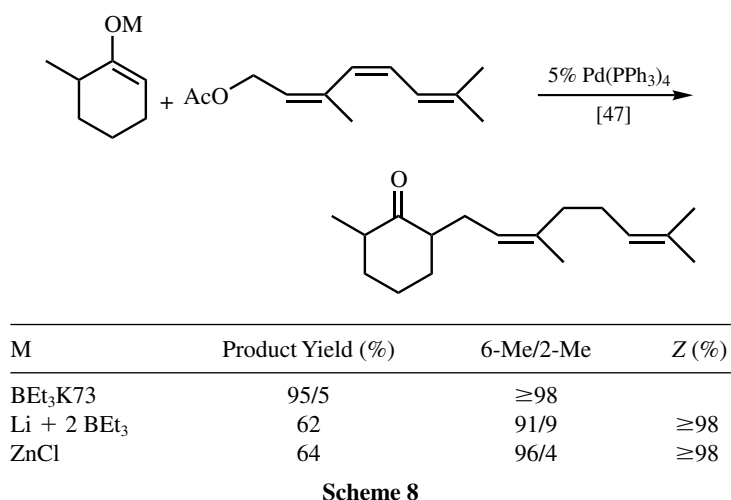




Scheme 7 (Continued)

Organozincs have been shown to be generally satisfactory cross-coupling partners with acyl chlorides under the influence of Pd catalysts. Grignard reagents are known to undergo uncatalyzed reactions with acyl halides. This reaction, however, tends to give tertiary alcohols. Organoboron compounds do not appear to undergo satisfactorily the Pd-catalyzed acylation,<sup>[54]</sup> even though the uncatalyzed acylation of alkylborates<sup>[63]</sup> is known. The use of basic conditions that would complicate the desired acylation with acyl chlorides and some side reactions of organoborons with acyl halides appear to be complicating factors.

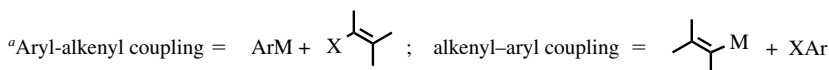
Finally, metal enolates containing Zn, B, and Sn have been shown to be applicable to the Pd-catalyzed  $\alpha$ -substitution of enolates. In particular, the Pd-catalyzed allylation of enolates containing Zn or B is generally favorable and complementary with the conventional alkali metal-based methodology in that (i) a much wider range of allylic derivatives can be used and (ii) the reactivity order among various allylic electrophiles is sometimes reversed<sup>[47],[64],[65]</sup> (**Scheme 8**). In this connection, a pioneering study of  $\alpha$ -arylation and  $\alpha$ -alkenylation of the Reformatsky reagents using both Ni and Pd catalysts by Fauvarque and Jutand<sup>[66]–[68]</sup> is noteworthy (**Scheme 9**). These reactions along with related others are discussed further in **Sect. III.14.1**.



The foregoing discussions are summarized in **Table 1** to provide a bird's-eye view of the synthetic applicability of Pd-catalyzed cross-coupling of organozincs *vis-à-vis* those organometals containing B, Sn, Mg, Al, Zr, and others. The major criteria include (i) catalytic reactivity, (ii) general scope, (iii) product yields, and (iv) stereoselectivity. In the following section, some other factors will be discussed.

**TABLE 1. Scope of Pd-Catalyzed Cross-Coupling of Organozincs and Their Alternatives**

Type of Cross-Coupling <sup>a</sup>	General Comment on Organozincs	Alternatives
Aryl–Aryl (Sect. III.2.5)	One of the three mostly favorable	B and Sn are highly competitive; Mg should not be overlooked
Aryl–Alkenyl Alkenyl–Aryl Alkenyl–Alkenyl (Sects. III.2.6 and III.2.7)	Generally most favorable especially in demanding alkenyl–alkenyl coupling	B(+base), Al(+ZnX <sub>2</sub> ), Zr(+ZnX <sub>2</sub> ), Sn, Cu(+ZnX <sub>2</sub> ), Mg, and Si(+F) are worthy alternatives, when applicable
Use of RC≡CM (Sect. II.2.8)	Generally satisfactory and most favorable	Mg and Cu (Sonogashira) should be checked first; B and Sn have been satisfactory in less demanding cases
Use of ArCH <sub>2</sub> M and ArCH <sub>2</sub> X (Sects. III.2.9 and III.2.10)	Generally favorable; ArCH <sub>2</sub> ZnX are probably the most favorable	Several other metals are competitive in some cases
Use of  X (Sects. III.2.9 and III.2.10)	Generally favorable	B and Sn are highly competitive
Use of  M (Sects. III.2.9 and III.2.10)	Generally unfavorable	Organotinns have provided some satisfactory results, but Cu without Pd catalysts should be considered first
Use of alkylM (Sect. III.2.11)	Satisfactory if Me, primary, homoallyl, homopropargyl, and homobenzyl derivatives are used; secondary and tertiary alkyl may undergo isomerization	Mg should be considered, when RZnX is prepared via RMgX; B is often competitive especially if alkylboranes are available via hydroboration; the scope with Sn is limited
Acylation (Sect. III.2.12.1)	Generally satisfactory; probably the most general	Sn is often competitive; B has hardly been used
Use of enolate (Sect. III.2.14.1)	Most promising along with B and Sn; needs further investigations	B and Sn are competitive



## B. VARIOUS OTHER FACTORS AND PARAMETERS FOR THE COMPARISON OF THE NEGISHI PROTOCOL WITH OTHER PROTOCOLS

In the foregoing discussions, the catalytic reactivity is the major criterion for the comparison of various metals. However, the overall evaluation of the merits and demerits of

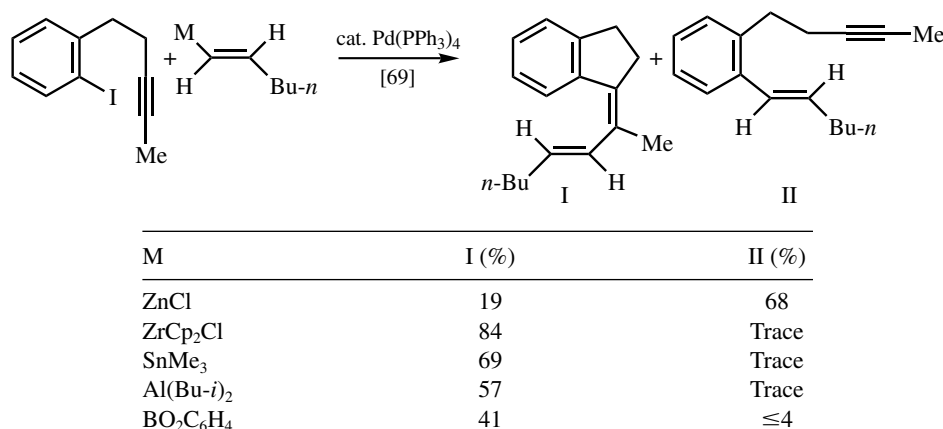
various competing protocols must not depend on the reactivity alone. Other important factors include (i) accessibility, including the ease of preparation of the required organometals, (ii) various other important chemical aspects, such as chemoselectivity, stereoselectivity, and regioselectivity, (iii) various technical aspects, such as operational simplicity and safety, including toxicity issues, and (iv) other practically important aspects, such as cost. For example, the relatively high toxicity associated with Sn has been a serious concern. Likewise, potential fire hazard associated with the use of flammable organometals including those containing Li, Mg, Zn, B, and Al is a serious technical and safety concern. Although a systematic discussion of these aspects is rather difficult, further comparison of Zn with several others used widely in Pd-catalyzed cross-coupling is briefly presented below.

### B.i. Contrasting Chemical Behaviors

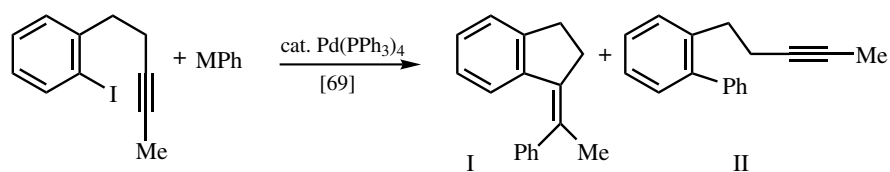
In some cases, different metals exhibit significantly different chemical behaviors, which do not necessarily pertain to the relative superiority or inferiority of various metals. Instead, they represent potentially useful differences that further diversify the scope of Pd-catalyzed cross-coupling. Some representative examples involving Zn are presented below.

In Pd-catalyzed cascading reactions where the cross-coupling reaction is to serve as the cascade-terminating step, the high reactivity of organozincs has interfered with such cascade processes by short-circuiting the desired cascade. In such cases, slower-reacting metals (e.g., B, Al, Sn, and Zr) have been shown to be significantly better than Zn<sup>[69]</sup> (**Scheme 10**). Other related results without comparative data are also known.<sup>[70]–[72]</sup> Despite this limitation associated with Zn, it should, at the same time, be clearly noted that the cross-coupling reaction of organozincs can preferentially proceed in competition with intramolecular cyclic carbopalladation.

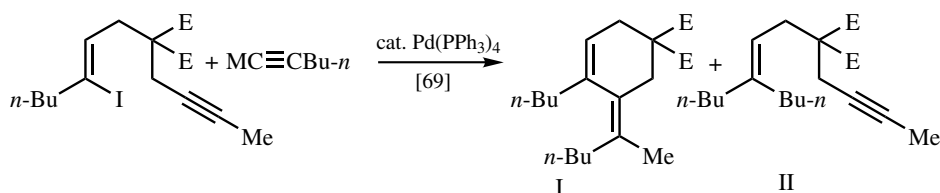
Similarly, the high reactivity of organozincs tends to preclude the CO insertion–cross-coupling tandem process, which proceeds well with slower reacting organotin.<sup>[73]–[75]</sup> However, some chelation-stabilized alkylzinc derivatives do satisfactorily participate in this tandem process<sup>[76]</sup> (**Scheme 11**). It should also be recalled that the Pd-catalyzed reaction of organozincs with acyl halides without the use of CO is one of the most general routes to ketones.<sup>[14]</sup>



Scheme 10

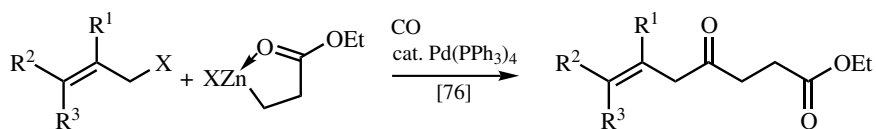


M	I (%)	II (%)
ZnCl	34	57
AlPh <sub>2</sub>	93	<2
SnBu <sub>3</sub>	Trace	Trace



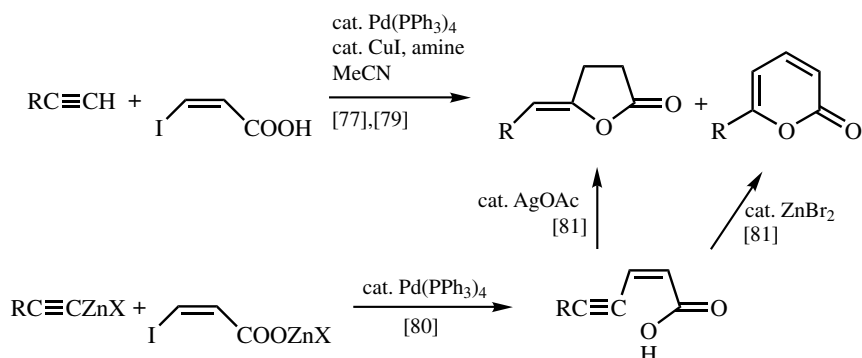
M	I (%)	II (%)
ZnC≡CBu- <i>n</i>	8	75
SnBu <sub>3</sub>	73	<5
BBu <sub>3</sub> Li	45	—
H(+ CuL + BuNH <sub>2</sub> )	16	49

Scheme 10 (Continued)



Scheme 11

Yet another striking contrast has been observed in the Pd-catalyzed reaction of (*Z*)- $\beta$ -haloacrylic acids with alkynyl nucleophiles. With terminal alkynes, the reaction run under the Sonogashira conditions proceeds to give (*Z*)- $\gamma$ -alkyldenebutenolides along with variable amounts of the corresponding pyrones.<sup>[77]–[79]</sup> In sharp contrast, the Pd-catalyzed reaction of alkynylzinc derivatives produces the desired cross-coupling products in good yields.<sup>[80]</sup> Most interestingly, the enynic acids thus obtained can now be selectively cyclized in nearly quantitative yields to give either (*Z*)- $\gamma$ -alkyldenebutenolides or pyrones<sup>[81]</sup> (**Scheme 12**).



Scheme 12

**B.ii. Accessibility**

Organometals required in Pd-catalyzed cross-coupling are generally prepared by several of a dozen or so general methods for the preparation of organometals<sup>[82]</sup>: (i) transmetalation, (ii) oxidative metallation, (iii) hydrometallation, (iv) carbometallation, and (v) heterometallation including metallometallation. In **Table 2**, a rough summary of the applicability of these methods to the synthesis of organometals containing Zn,<sup>[83]</sup> B,<sup>[53],[54]</sup> and Sn<sup>[84],[85]</sup> are presented. These reactions are further discussed throughout this Handbook.

**TABLE 2. Preparation of Organometals Containing Zn, B, Sn, and Other Metals**

Method	Zn	B	Sn	Other
Transmetalation (with RLi or RMgX)	Generally applicable, operationally simple	Generally applicable but can be operationally complicated	Generally applicable	Of limited applicability with Zr
Oxidative Metallation	Promising new development	Pd-catalyzed reaction with X <sub>2</sub> BBX <sub>2</sub> promising but expensive	Pd-catalyzed reaction with R <sub>3</sub> SnSnR <sub>3</sub> promising but expensive	Some are known for Al and Zr
Hydrometallation	Some known but further development needed	Most general and most dependable	Some are useful; needs to be developed further to be generally applicable	Hydroalumination and hydrozirconation useful but not as general as hydroboration
Other additions	Carbozincation very promising	Haloboration of alkynes generally satisfactory		

As can be seen from **Table 2**, the organometals containing Zn, B, and Sn may be judged to be comparably accessible. Organozincs have become much more widely accessible by recently developed direct oxidative metallation and carbozincation reactions,<sup>[83],[86]</sup> while hydroboration<sup>[87]</sup> and haloboration<sup>[88]</sup> provide uniquely advantageous routes to organoboranes. Although hydrostannation is not nearly as general and dependable as hydroboration, the Pd-catalyzed stannation of organic halides<sup>[85]</sup> is a promising route to organostannanes. A related boron reaction<sup>[89]</sup> has also been recently developed.

### B.iii. Chemoselectivity

The high chemoselectivity of organoborons and organotins in a conventional sense has been strongly emphasized, and these classes of organometals can indeed tolerate many electrophilic heteroatom functional groups that Grignard reagents and organolithiums cannot. What might not have been portrayed accurately is the surprisingly high chemoselectivity of organozincs in a conventional sense.<sup>[83]</sup> They can generally tolerate (i) most of the carbonyl-containing functional groups except acyl halides and aldehydes that include ketones, carboxylic acid (after metallation), esters, amides, and so on, (ii) nitriles, (iii) nitro, (iv) less reactive halogens (e.g., F, Cl, and Br) in some cases, (v) oxy, (vi) amino, and other heteroatom groups in organic electrophiles. Furthermore, the direct zincation of organic halides has tolerated many of these functional groups in the organozinc reagents themselves.<sup>[83]</sup> It has also been often overlooked that Pd-catalyzed organoboron coupling reactions are mostly carried out in the presence of oxy bases (e.g., NaOH and NaOMe). Consequently, the chemoselectivity associated with organoborons must include that of added bases as well. Overall, it is reasonable to sum up that, unlike Grignard reagents and organolithiums, organozincs are rather chemoselective in a conventional sense even in comparison with organoborons and organostannanes. One significant difference between Zn and B or Sn, however, is that, whereas organometals containing B and Sn are mostly stable to H<sub>2</sub>O and alcohols, organozincs are generally not. This precludes Pd-catalyzed cross-coupling of organozincs under aqueous and related protic conditions.

### B.iv. Other Factors

Organozincs must be regarded as being air- and moisture-sensitive and handled accordingly. While tri- and diorganylboranes are air-sensitive, monoorganylboranes (e.g., boric acids and esters) are often air- and moisture-stable. Similarly, organostannanes are generally air- and moisture-stable. On the other hand, zinc-containing by-products, mainly zinc salts, are generally water soluble and readily separable by aqueous workup. On the other hand, tin-containing by-products are usually soluble in organic solvents, and they tend to elute over a wide range in chromatography. So, their complete removal from the desired products is often difficult. In the cases of organoborons, oxidative workup converts essentially all boron compounds into boric acid, which can then be readily separated from the organic products. The operational problem associated with organotins is compounded by the relatively high toxicity of organotins. On the other hand, boric acids and zinc salts are generally of low toxicity. It should be recalled that Zn is essential to human and other biological functions.

Comparison of relative costs of various metals is not straightforward. Zinc salts (i.e., ZnCl<sub>2</sub> and ZnBr<sub>2</sub>) as well as boric esters and Bu<sub>3</sub>SnCl may be judged to be relatively inexpensive. However, value-added B- and Sn-containing compounds, such as various hydridoboranes, B—B bond-containing compounds, Me<sub>3</sub>SnCl, and distannanes

(i.e.,  $R_3SnSnR_3$ ), can be substantially more expensive than some of the least expensive B and Sn compounds. The cost factor must be carefully monitored along with all of the other factors discussed in this section.

### C. SUMMARY

1. The Pd-catalyzed cross-coupling of organozincs provides a highly desirable combination of a high catalytic reactivity and a reasonably high chemoselectivity, and it has displayed the widest overall synthetic scope. As summarized in **Table 1**, it is either most favorable or comparable with some of the best protocols in nearly all categories of Pd-catalyzed cross-coupling. Interestingly, even some of its limitations stem from the high catalytic reactivity of organozincs.

2. Organozincs are mainly prepared by transmetallation reactions of organolithiums and Grignard reagents, although direct zincation, hydrozincation, and carbozincation promise to provide more chemoselective routes to organozincs. In cases where Grignard reagents are used as precursors to organozincs, it is well worth testing the Pd-catalyzed coupling reaction of Grignard reagents themselves, as it is a more direct and operationally somewhat simpler method.

3. In cases where hydrometallation, carbometallation, heterometallation, and metal-lometallation involving B, Al, Sn, Cu, and Zr provide satisfactory routes to the required organometals, they may prove to be more satisfactory and desirable than the organozinc reaction. If those reactions involving Al, Cu, and Zr should prove to be sluggish, addition of  $ZnCl_2$  or  $ZnBr_2$  can accelerate such reactions. Alternatively, the corresponding organozincs may be prepared via iodidation and metallation and used in the Pd-catalyzed reaction for attaining the highest catalytic reactivity. An increasing number of cases that benefit from the Zn alternatives are being found.

4. The Pd-catalyzed cross-coupling with alkynylzincs appears to be considerably more general than the Sonogashira alkynylation. However, the operational simplicity may favor the latter in most of those cases where both are comparably satisfactory. On the other hand, there have been an increasing number of cases where the alkynylzinc reaction is decidedly more favorable than the Sonogashira reaction.

5. Selection of B, Sn, and some other metals, such as Al, Zr, Cu, and Si, over Zn in the other categories should be made with rational and sensible justifications in view of the competitive accessibility of organozincs, the operational simplicity, the relative low cost, and the low toxicity associated with organozincs.

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