

# MAGICAL POWER OF TRANSITION METALS: PAST, PRESENT, AND FUTURE

Nobel Lecture, December 8, 2010

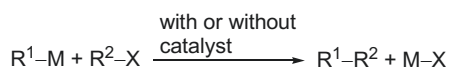
by

EI-ICHI NEGISHI

Herbert C. Brown Laboratories of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, IN 47907-2084, U.S.A.

Not long ago, the primary goal of the synthesis of complex natural products and related compounds of biological and medicinal interest was to be able to synthesize them, preferably before anyone else. While this still remains a very important goal, a number of today's top-notch synthetic chemists must feel and even think that, given ample resources and time, they are capable of synthesizing virtually all natural products and many analogues thereof. Accepting this notion, what would then be the major goals of organic synthesis in the twenty-first century? One thing appears to be unmistakably certain. Namely, we will always need, perhaps increasingly so with time, the uniquely creative field of synthetic organic and organometallic chemistry to prepare both new and existing organic compounds for the benefit and well-being of mankind. It then seems reasonably clear that, in addition to the question of what compounds to synthesize, that of how best to synthesize them will become increasingly important. As some may have said, the primary goal would then shift from aiming to be the first to synthesize a given compound to seeking its ultimately satisfactory or "last synthesis".

If one carefully goes over various aspects of organic synthetic methodology, one would soon note how primitive and limited it had been until rather recently, or perhaps even today. For the sake of argument, we may propose here that the ultimate goal of organic synthesis is "*to be able to synthesize any desired and fundamentally synthesizable organic compounds (a) in high yields, (b) efficiently (in as few steps as possible, for example), (c) selectively, preferably all in  $\geq 98$ –99% selectivity, (d) economically, and (e) safely, abbreviated hereafter as the y(es)<sup>2</sup> manner.*"



R<sup>1</sup>, R<sup>2</sup>: carbon groups. M: metal or metal-containing groups.

X: halogens or other leaving groups.

*Scheme 1.*






$R^2X$ $R^1M$	ArX						Alkyl X	RCOX
ArM	<ul style="list-style-type: none"> <li>• These reactions do not proceed except in special cases</li> </ul>						Limited scope	Needs special procedures
								
								
								
								
								
Alkyl M								
N≡C-M								
								

Table 1. Scope and Limitations of Uncatalyzed Cross-Coupling with Grignard Reagents and Organoalkali Metals.

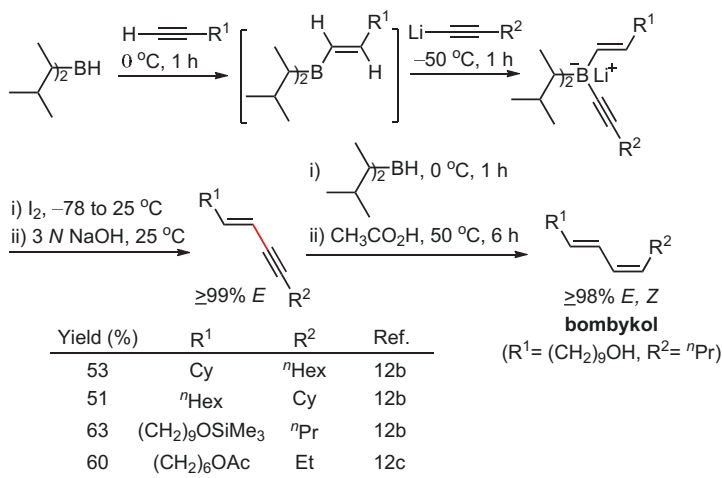
Half a century ago, however, only a limited number of cases of cross-coupling reactions using Grignard reagents and related organoalkali metals containing Li, Na, K and so on were known. Their reactions with sterically less hindered primary and some secondary alkyl electrophiles ( $R^2X$ ) are generally satisfactory. Even so, the overall scope of their cross-coupling reactions was severely limited. One of their most serious limitations was their inability to undergo satisfactory C–C bond formation with unsaturated  $R^2X$  containing unsaturated carbon groups, such as aryl, alkenyl, and alkynyl groups, with some exceptions<sup>1</sup> (Table 1).

## EVOLUTION OF THE Pd-CATALYZED CROSS-COUPLING

The cross-coupling methodology has evolved mainly over the past four decades into one of the most widely applicable methods for C–C bond formation, that is centered around the Pd-catalyzed cross-coupling with organometals containing Al, Zn, Zr (Negishi coupling),<sup>2, 3</sup> B (Suzuki coupling),<sup>2, 4</sup> and Sn (Stille coupling)<sup>2, 5</sup> as well as those containing several other metals including Cu,<sup>6</sup> In,<sup>7</sup> Mg,<sup>8</sup> Mn,<sup>9</sup> and Si<sup>10</sup> (Hiyama coupling). Although of considerably more limited scope, both the seminal

nature of the Ni-catalyzed Grignard cross-coupling of Tamao and Kumada<sup>11a, 11b</sup> as well as of Corriu<sup>11c</sup> and its sustained practical synthetic values must not be overlooked in cases where its overall synthetic merits are comparable with or even superior to those Pd-catalyzed reactions mentioned above.

Evolution within the author's group actually began with the development of some selective C–C bond formation reactions of alkenylboranes leading to most probably the earliest highly selective ( $\geq 98\%$ ) syntheses of unsymmetrically substituted conjugated (*E, E*)- and (*E, Z*)-dienes,<sup>12</sup> following the pioneering studies of alkyne hydroboration by Brown<sup>13</sup> and subsequent C–C bond formation by Zweifel<sup>14</sup> (Scheme 2).



Scheme 2.

Despite these successes, however, the author's group concurrently began exploring the possibility of promoting the C–C bond formation with alkenylboranes and alkenylborates with some transition metals. After a series of total failures with some obvious choices then, namely a couple of cuprous halides, which were later shown to be rather impure, our attention was turned to a seminal publication of Tamao reporting the Ni-catalyzed Grignard cross-coupling (Tamao-Kumada-Corriu coupling).<sup>11</sup> Our quixotic plans for substituting Grignard reagents with alkenylboranes and alkenylborates were uniformly unsuccessful.<sup>15</sup> In retrospect, it must have been primarily due to the fact that all of our experiments were run at 25 °C in THF. As soon as we replaced alkenylboron reagents with alkenylalanes, however, smooth Ni-catalyzed cross-coupling reactions of (*E*)-1-alkenyldiisobutylalanes with several aryl bromides and iodides took place to provide the cross-coupling products of  $\geq 99\%$  *E* geometry.<sup>15a</sup> The corresponding Pd-catalyzed reactions were also observed but no apparent advantage in the use of Pd(PPh<sub>3</sub>)<sub>4</sub> in place of Ni(PPh<sub>3</sub>)<sub>4</sub> was noticed. One of our main goals was to be able to synthesize stereo- and regio-defined conjugated dienes. Indeed, both Ni- or Pd-catalyzed

cross-coupling of alkenylalanes with alkenyl iodides proceeded as desired.<sup>15b</sup> In these reactions, however, the Pd-catalyzed reactions were distinctly superior to the corresponding Ni-catalyzed reactions in that the Pd-catalyzed reactions retained the original alkenyl geometry to the extent of  $\geq 97\%$ , mostly  $>99\%$ , whereas the corresponding Ni-catalyzed reactions showed the formation of undesirable stereoisomers up to  $10\%$ .<sup>15b</sup> Our literature survey revealed that there was one paper by Murahashi<sup>8a</sup> reporting 4 cases of the Pd-catalyzed Grignard cross-coupling in 1975. We later learned that two other contemporaneous papers by Ishikawa<sup>8c</sup> and Fauvarque<sup>8d</sup> published in 1976 also reported examples of the Pd-catalyzed variants of the Ni-catalyzed Grignard cross-coupling. With our two papers published in 1976,<sup>15</sup> *we thus reported, for the first time, Ni- and Pd-catalyzed cross-coupling reactions of non-Grignard reagents, namely organoalanes. Significantly, some unmistakable advantages associated with Pd over Ni were also recognized for the first time.*<sup>15b</sup>

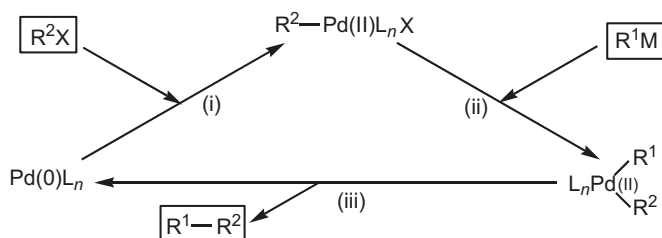
Sensing that the major player in the Pd-catalyzed cross-coupling might be Pd rather than the stoichiometric quantity of a metal counteranion (M) and that the main role of M of R<sup>1</sup>M in Scheme 1 might be to effectively feed R<sup>1</sup> to Pd, ten or so metals were screened by using readily preparable 1-heptynylmetals containing them. As summarized in Table 2,<sup>3a,16</sup> we not only confirmed our earlier finding that Zn was highly effective<sup>8c</sup> but also found that B and Sn were nearly as effective as Zn, even though their reactions were much slower. We then learned that examples of Pd-catalyzed cross-coupling with allyltins by Kosugi<sup>5b</sup> had been reported a year earlier 1977 but that *the reaction of the borate marked the discovery of the Pd-catalyzed organoboron cross-coupling.* As is well known, extensive investigations of the Pd-catalyzed cross-coupling reactions of organometals containing B by Suzuki<sup>4c,4d</sup> and Sn by Stille<sup>5c,5d</sup> began in 1979.

$n\text{PentC}\equiv\text{CM} + \text{I-C}_6\text{H}_4\text{CH}_3 \xrightarrow[\text{THF}]{\text{cat. PdL}_n} n\text{PentC}\equiv\text{C-C}_6\text{H}_4\text{CH}_3$

M	temp (°C)	time (h)	product yield (%)	starting material (%)
Li	25	1	trace	88
Li	25	24	3	80
MgBr	25	24	49	33
ZnCl	25	1	91	8
HgCl	25	1	trace	92
HgCl	reflux	6	trace	88
BBu <sub>3</sub> Li	25	3	10	76
BBu <sub>3</sub> Li	reflux	1	92	5
Al <sup>i</sup> Bu <sub>2</sub>	25	3	49	46
AlBu <sub>3</sub> Li	25	3	4	80
AlBu <sub>3</sub> Li	reflux	1	38	10
SiMe <sub>3</sub>	reflux	1	trace	94
SnBu <sub>3</sub>	25	6	83	6
ZrCp <sub>2</sub> Cl	25	1	0	91
ZrCp <sub>2</sub> Cl	reflux	3	0	80

Table 2. Reactions of 1-Heptynylmetals with *o*-Tolyl Iodide in the Presence of Cl<sub>2</sub>Pd(PPh<sub>3</sub>)<sub>2</sub> and *i*Bu<sub>2</sub>AlH

On the basis of a “three-step” mechanism consisting of (i) oxidative addition of  $R^2X$  to  $Pd(0)L_n$  species, where  $L_n$  represents an ensemble of ligands, (ii) transmetalation between  $R^2Pd(II)L_nX$  and  $R^1M$ , and (iii) reductive elimination of  $R^1R^2Pd(II)L_n$  to give  $R^1R^2$  (Scheme 3) widely accepted as a reasonable working hypothesis,<sup>3-5,8,11</sup> we reasoned that, as long as all three microsteps are kinetically accessible, the overall process shown in Scheme 1 would be thermodynamically favored in most cases by the formation of  $MX$ . In view of the widely observed approximate relative order of reactivity of common organic halides toward  $Pd(0)$  complexes also indicated in Scheme 3, a wide range of  $Pd$ -catalyzed cross-coupling reactions of aryl, alkenyl, alkynyl, benzyl, allyl, propargyl, and acyl halides and related electrophiles ( $R^2X$ ) as well as  $R^1M$  containing these carbon groups were further explored. In view of distinctly lower reactivity of alkyl halides including homobenzylic, homoallylic, and homopropargylic electrophiles, the use of alkylmetals as  $R^1M$  was considered.



(i) oxidative addition, (ii) transmetalation, (iii) reductive elimination  
 $R^1, R^2 = C$  groups.  $X = I, Br, Cl, OTf, etc.$   $M =$  metal counterion.

**Approximate Relative Order of Reactivity of Organic Halides in Oxidative Addition to Pd**

Allyl > Benzyl > Alkenyl > Aryl >> simple Alkyl  
 Propargyl > Acyl > Alkynyl

*Scheme 3.*

A couple of dozen papers published by us during the first several years of the 1980s on  $Pd$ -catalyzed (i) alkylation with alkylmetals,<sup>17</sup> (ii) cross-coupling between aryl, alkenyl, or alkynyl groups and benzyl, allyl, or propargyl groups,<sup>18</sup> (iii) the use of heterosubstituted aryl, alkenyl, and other  $R^1M$  and  $R^2M$ ,<sup>17d,19</sup> as well as acyl halides,<sup>20</sup> and (iv) allylation of metal enolates containing  $B$  and  $Zn$  that are not extra-activated by the second carbonyl group<sup>21</sup> amply supported the optimistic notion that the  $Pd$ -catalyzed cross-coupling might be very widely applicable with respect to  $R^1$  and  $R^2$  to be cross-coupled.

**CURRENT PROFILE OF THE  $Pd$ -CATALYZED CROSS-COUPLING**

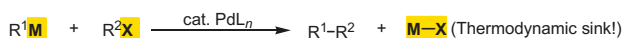
Today, the overall scope of the  $Pd$ -catalyzed cross-coupling may be shown as summarized in Table 3. Although any scientific progress is evolutionary,

comparison of Table 3 with Table 1 does give us an impression that the progress made in this area has been rather revolutionary. Regardless, it would represent one of the most widely applicable methods for C–C bond formation that has begun rivaling the Grignard- and organoalkali metal-based conventional methods as a whole for C–C bond formation. Much more importantly, these two methods – one modern and the other conventional – are mostly complementary rather than competitive with each other. As is clear from Table 3, a little more than half of the seventy-two classes of cross-coupling listed in Table 3 generally results not only in high yields but also in high selectivity ( $\geq 98\%$ ) in most of the critical respects. In approximately twenty other classes of cross-coupling, the reactions generally result in high overall yields, but some selectivity features need to be further improved. Only the remaining dozen or so classes of cross-coupling reactions either have remained largely unexplored or require major improvements. Fortunately, in most of these three dozen or so less-than-satisfactory cases, the Pd-catalyzed cross-coupling methodology offers satisfactory alternatives requiring modifications as simple as (a) swapping the metal (M) and the leaving group (X), (b) shifting the position of C–C bond formation by one bond, and (c) using masked or protected carbon groups, as exemplified later.

At this point, it is useful to briefly discuss some of the fundamentally important factors contributing to the current status of the Pd-catalyzed cross-coupling.

**(1) Use of metals (M) of moderate electronegativity represented by Zn.** The transition metal-catalyzed cross-coupling may have started as Grignard or organoalkali metal reactions with organic electrophiles to which transition metal-containing compounds were added in the hope of catalyzing or promoting such reactions. The earlier seemingly exclusive use of Grignard reagents and organoalkali metals as  $R^1M$  in Scheme 1 strongly suggests that their high intrinsic reactivity was most probably thought to be indispensable. In reality, however, there have been a rather limited number of publications on the reactions of organoalkali metals catalyzed by Pd complexes,<sup>8b,22</sup> and the results are mostly disappointing except in some special cases. The current profile of the Pd- or Ni-catalyzed Grignard cross-coupling is considerably more favorable.<sup>8,11</sup> In the overall sense, however, its scope is significantly more limited than those employing Zn and B supplemented with Al and Zr. It has become increasingly apparent that Grignard reagents and organoalkali metals are intrinsically too reactive to allow Pd to efficiently participate in the putative three-step catalytic cross-coupling cycle (Scheme 3). Indeed, under stoichiometric conditions, alkali metals and Mg are often as effective as or even more effective than Zn and other metals.<sup>23</sup> These results suggest that their excessive reactivity may serve as Pd-catalyst poisons. Another major difficulty with Grignard reagents and organoalkali metals is their generally low chemoselectivity in the conventional sense. As one of the important advantageous features of the Pd-catalyzed cross-coupling is that it permits pre-assembly of functionally elaborated  $R^1M$  and  $R^2X$  for the final or nearly final assemblage of  $R^1-R^2$ , the low chemoselectivity of Grignard reagents

and organoalkali metals is a critically serious limitation. Despite these shortcomings, however, the Pd- or Ni-catalyzed Grignard cross-coupling<sup>8,11</sup> should be given a high priority in cases where it is competitively satisfactory in the overall sense, because Grignard reagents often serve as precursors to other organometals. In the other cases, metals of moderate electronegativity (1.4–1.7), such as Zn (1.6), Al (1.5), In (1.7), and Zr (1.4), where the numbers in parentheses are the Pauling electronegativity values, should offer a combination of superior reactivity under Pd-catalyzed conditions and high chemoselectivity. The surprisingly high chemoselectivity of Zn has made it desirable to prepare organozincs without going through organoalkali metals or Grignard reagents, and intensive explorations by Knochel<sup>24</sup> are particularly noteworthy. Although B in boranes may be highly electronegative (2.0), rendering organoboranes rather non-nucleophilic, its electronegativity can be substantially lowered through borate formation. This dual character of B makes it an attractive metal in the Pd-catalyzed cross-coupling.<sup>4</sup>



$R^1, R^2 = \text{C group}$ . See below.  $M = \text{Mg, Zn, B, Al, In, Si, Sn, Cu, Mn, Zr, etc.}$   $X = \text{I, Br, Cl, F, OTs, OTf, etc.}$

$M \ \& \ X = \text{Regio- \& stereo-specifiers, which permit a genuine LEGO Game avoiding addition-elimination.}$








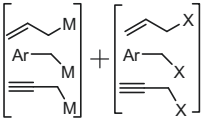




$R^1M \backslash R^2X$	ArX						Alkyl X	RCOX
ArM							<ul style="list-style-type: none"> <li>• Little known until recently</li> <li>• Recent results promising</li> <li>• Consider AlkylM as alternatives</li> <li>• Consider also uncatalyzed and Cu-, Ni-, or Fe-catalyzed processes</li> </ul>	
								
								
Ar-M							<div style="border: 1px solid red; padding: 5px; display: inline-block;">  </div> <p>Use the alternate routes shown below</p>	
	Use alternate routes. Follow the arrow							
								
Alkyl M								
N=C-M								
	Use of $\alpha$ -haloenones as enolate equivalents should be considered				Tsuji-Trost Reaction			

Table 3. LEGO Game Approach to C–C Bond Formation via Pd-Catalyzed Cross-Coupling Reactions.

**(2) Pd as the optimal catalyst component.** Although Cu,<sup>25</sup> Ni,<sup>11,15,26,27</sup> Fe,<sup>28</sup> and even some other *d*-block transition metals have been shown to be useful elements in C–C cross-coupling, it is Pd that represents the currently most widely useful catalyst in catalytic cross-coupling. In a nutshell, it shares with other transition metals some of the crucially important features, such as an ability to readily interact with non-polar  $\pi$ -bonds, such as alkenes, alkynes, and arenes, leading to facile, selective, and often reversible oxidative addition, transmetalation, and reductive elimination shown in Scheme 3.

In contrast with the high reactivity of proximally  $\sigma$ -bonded organic halides, most of the traditionally important heteroatom-containing functional groups, such as various carbonyl derivatives except acyl halides, are much less reactive toward Pd, and their presence is readily tolerated. These non-conventional reactivity profiles associated with some *d*-block transition metals have indeed provided a series of new and general synthetic paradigms involving transition metal catalysts, such as Pd-catalyzed cross-coupling and olefin metathesis.<sup>29</sup>

But, why is Pd so well suited for transition metal-catalyzed cross-coupling? If we compare Pd with the other two members of the Ni triad, the heavier and larger Pt is also capable of participating in the three microsteps in Scheme 3, but  $R^1R^2PtL_n$  are much more stable than the corresponding Pd- or Ni-containing ones, and their reductive elimination is generally too slow to be synthetically useful, even though fundamentally very interesting.<sup>30</sup> On the other hand, smaller Ni appears to be fundamentally more reactive and versatile than Pd. Whereas Pd appears to strongly favor the 0 and +2 oxidation states separated by two electrons, Ni appears to be more prone to undergoing one-electron transferring redox processes in addition to the desired two electron redox processes, leading to less clean and more complex processes. Our recent comparisons of the TONs of various classes of Ni- and Pd-catalyzed cross-coupling reactions between two unsaturated carbon groups<sup>31,32</sup> have indicated that the Ni-catalyzed reactions generally display lower TONs by a factor of  $\geq 10^2$  and lower levels of retention of stereo- and regiochemical details, readily offsetting advantages stemming from the lower cost of Ni relative to Pd. On the other hand, cleaner Pd-catalyzed cross-coupling reactions often display TONs of  $\geq 10^6$ . In some cases, TONs reaching or even surpassing  $10^9$  have been observed.<sup>32</sup> Thus, for example, the reactions of phenylzinc bromide with *p*-iodotoluene and of (*E*)-1-decenylyzinc bromide with iodobenzene in the presence of  $Cl_2Pd(DPEphos)$  in THF exhibited TONs of  $9.7 \times 10^9$  and  $8.0 \times 10^7$ , respectively, while producing the desired products in  $\geq 97\%$  and 80% yields, respectively.<sup>32</sup> At these levels, not only cost issues but also some alleged Pd-related toxicity issues should become significantly less serious.

**(3) Critical comparison of  $R^1M$  and  $R^1H$ .** It is generally considered that the use of  $R^1H$  in place of  $R^1M$  would represent a step in the right direction toward “green” chemistry. This statement would be correct and significant provided that all of the other things and factors are equal or comparable. In reality, however, the other things and factors are rarely equal or comparable,



and valid comparisons must be made by taking into consideration all significant factors. In Pd-catalyzed alkenylation and also alkynylation, development of Pd-catalyzed cross-coupling versions using Zn, B, Sn, and others as M in R<sup>1</sup>M were, in fact, preceded by the R<sup>1</sup>H versions, namely Heck alkenylation<sup>33</sup> and Heck-Sonogashira alkynylation.<sup>34</sup> Thus, evolution of the cross-coupling version took place in the R<sup>1</sup>H-to-R<sup>1</sup>M, rather than R<sup>1</sup>M-to-R<sup>1</sup>H, direction. Despite some inherent advantages associated with the R<sup>1</sup>H versions over the corresponding R<sup>1</sup>M versions, the synthetic scopes of the R<sup>1</sup>H versions are generally significantly more limited than the R<sup>1</sup>M versions.<sup>35</sup> From the perspective of synthesizing conjugated di- and oligoenes in the  $\gamma(\text{es})^2$  manner, the following difficulties and limitations of Heck alkenylation must be noted.

- i. need for certain activated and relatively unhindered alkenes, such as styrenes and carbonyl-conjugated alkenes, for satisfactory results,<sup>36</sup>
- ii. inability to produce either pure ( $\geq 98\%$ ) *E* or *Z* isomer from a given alkene used as R<sup>1</sup>H which can be readily and fully overcome by the use of stereo-defined isomerically pure ( $\geq 98\%$ ) alkenylmetals as R<sup>1</sup>M,<sup>37</sup>
- iii. frequent formation of undesirable regioisomeric and stereoisomeric mixtures of alkenes<sup>33,37</sup> leading to lower yields of the desired alkenes, and
- iv. lower catalyst TONs (typically  $\leq 10^2$ – $10^3$ ) except for the syntheses of styrenes having an additional aryl, carbonyl, or proximal hetero-functional group<sup>33c</sup> as compared with those often exceeding  $10^6$  for the corresponding R<sup>1</sup>M version, especially with Zn as M,<sup>32</sup> significantly affecting cost and safety factors.

Both the fundamental and practical merits of using metals (M) as (a) regio- and stereo-specifiers, (b) kinetic activators, and (c) thermodynamic promoters are abundantly clear, and these differences must not be overlooked. Of course, in those specific cases where the R–H versions of alkenylation and alkynylation are more satisfactory than the R<sup>1</sup>M version in the overall sense including all  $\gamma(\text{es})^2$  factors, their use over the R<sup>1</sup>M versions may be well justified. Thus, it would still remain important and practically useful to continuously seek and develop additional R<sup>1</sup>H processes that would proceed in the  $\gamma(\text{es})^2$  manner and would be considered superior to the R<sup>1</sup>M version for a given synthetic task. After all, when one specific chemical transformation is desired, it is the best optimal process for that case rather than the process of the widest scope and general superiority, that is to be chosen.

**(4) Advantage associated with the two-stage (LEGO game) processes of the Pd-catalyzed cross-coupling.** In the Pd-catalyzed cross-coupling, the step of the final molecular assembly involves formation of a C–C single bond. As long as it proceeds with full retention of all structural details of the R<sup>1</sup> and R<sup>2</sup> groups of R<sup>1</sup>M and R<sup>2</sup>X, an isomerically pure single product (R<sup>1</sup>–R<sup>2</sup>) would be obtained except in those cases where formation of atropisomers are possible. While the majority of R<sup>1</sup> and R<sup>2</sup> groups do retain their structural details during Pd-catalyzed cross-coupling, allylic groups, especially allylic R<sup>1</sup>

in R<sup>1</sup>M, and propargyl groups as R<sup>1</sup> and/or R<sup>2</sup> may lose their regio- and/or stereochemical identities through allyl and propargyl–allenyl rearrangement, respectively. Secondary and tertiary alkyl groups are also prone to both stereoisomerization and β-elimination. However, some Pd- or Ni-catalyzed asymmetric alkylation has been reported to proceed stereoselectively.<sup>38</sup> Furthermore, the preparation of R<sup>1</sup>M and R<sup>2</sup>X can be performed in totally separate steps by using any known methods and, for that matter, any satisfactory methods yet to be developed in the future as well. Significantly, a wide range of R<sup>1</sup>M and R<sup>2</sup>X containing “sensitive” functional groups in a conventional sense, such as amides, esters, carboxylic acids, ketones, and even aldehydes, may be prepared and directly cross-coupled, as eloquently demonstrated by both regio- and chemoselective preparation and Pd-catalyzed cross-coupling of a wide range of aryl and related compounds, notably by Knochel<sup>24</sup> and Snieckus.<sup>39</sup>

As such, the two-stage processes for the synthesis of R<sup>1</sup>–R<sup>2</sup> offer certain distinct advantages over other widely used processes in which some critical structural features, such as chiral asymmetric carbon centers and geometrically defined C=C bonds, are to be established in the very steps of skeletal construction of the entire molecular framework. Such processes include an ensemble of conventional carbonyl addition and condensation (olefination) reactions as well as modern olefin metathesis.<sup>29</sup> For example, synthesis of (*Z*)-alkenes by intermolecular cross-metathesis has just made its critical first step<sup>40</sup> towards becoming a generally satisfactory route to (*Z*)-alkenes in the  $\gamma(\text{es})^2$  manner.

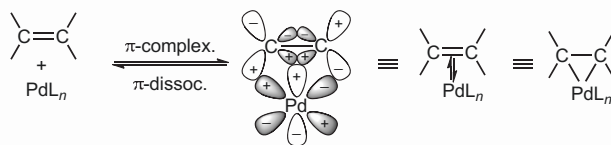
**(5) Why *d*-block transition metals? Some fundamental and useful structural as well as mechanistic considerations.** The three-step mechanistic hypothesis shown in Scheme 3 has provided reasonable bases not only for understanding various aspects of the seemingly concerted Pd-catalyzed cross-coupling but also for making useful predictions for exploring various types of concerted Pd-catalyzed cross-coupling reactions. Of course, what is shown in Scheme 3, which evolved from those seminal studies with Ni,<sup>11,41</sup> may be applicable to other transition metal-catalyzed processes. At the same time, it is important to be reminded that few mechanistic schemes have ever been firmly established and that they are, in most cases, not much more than useful working hypotheses for rational interpretations and predictions on the basis of the numbers of protons, electrons, and neutrons as well as space for accommodating them including orbitals accommodating electrons, which bring yet another fundamentally important factor, namely symmetry. The fundamental significance of the molecular orbital (MO) theory represented by the frontier orbital (HOMO–LUMO) theory of Fukui,<sup>42</sup> synergistic bonding of Dewar,<sup>43</sup> exemplified by the so-called Dewar–Chatt–Duncanson (DCD) model (Scheme 4), and the orbital symmetry theory of Woodward and Hoffmann<sup>44</sup> can never be overemphasized.

In the area of C–C cross-coupling in the  $\gamma(\text{es})^2$  manner with Pd and other *d*-block transition metals as the central catalyst components, at least the following two factors must be critically important:

- i. ability to provide simultaneously one or more each of valence-shell empty orbitals serving as LUMOs and filled non-bonding orbitals serving as HOMOs (Scheme 4) and
- ii. ability to participate in redox processes occurring simultaneously in both oxidative and reductive directions under one set of reaction conditions in one vessel.

The first of the two is partially shared by singlet carbenes and related species and therefore termed “carbene-like”. With one each of empty and filled non-bonding orbitals, carbenes are known to readily interact with non-polar  $\pi$ -bonds and even with some  $\sigma$ -bonds. The mutually opposite directions of HOMO–LUMO interactions which significantly minimize the effect of activation energy-boosting polarization in each HOMO–LUMO interaction should be firmly recognized. These features readily explain the facile and selective formation of stable  $\pi$ -complexes with  $d$ -block transition metals, which is not readily shared by main group elements, such as B and Al, as they cannot readily provide a filled non-bonding orbital together with an empty orbital.

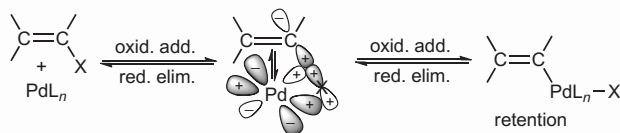
**Dewar-Chatt-Duncanson (D-C-D)  
Synergistic Bonding Scheme for  $\pi$ -Complexation–Dissociation**



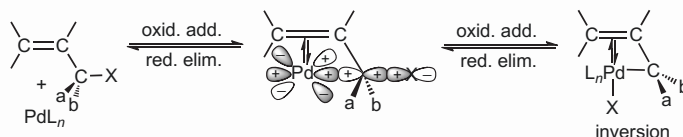
**Modified D-C-D Synergistic Bonding Scheme for  
Oxidative Addition – Reductive Elimination**



**$\pi$ -Complexation–Assisted Oxidative Addition with  
Alkenyl (Alkynyl or Aryl) Halides with Retention  
(D-C-D Synergistic  $\pi$ - and  $\sigma$ -Bonding Tandem)**



**$\pi$ -Complexation–Assisted Oxidative Addition with  
Allyl (Propargyl or Benzyl) Halides with Inversion  
(D-C-D Synergistic Bonding–Promoted 'S<sub>N</sub>2"-like Process)**



Scheme 4.









Despite the above-discussed similarity between carbenes and transition metals, there are some critically significant differences between them. Thus, *many transition metal-centered “carbene-like” species are not only of surprising thermal stability, even commercially available as chemicals of long shelf-lives at ambient temperatures, e.g., ClRh(PPh<sub>3</sub>)<sub>3</sub> and Cl<sub>2</sub>Pd(PPh<sub>3</sub>)<sub>2</sub>, but also reversibly formed in redox processes permitting high catalyst TONs often exceeding a million or even a billion.*<sup>31,32</sup> The authors are tempted to call such species “super-carbenoidal”. Significantly, the “super-carbenoidal” properties of *d*-block transition metals do not end here. In addition to numerous 16-electron species with one valence-shell empty orbital, there are a number of 14-electron species including surprisingly stable and even commercially available ones, such as Pd(<sup>t</sup>Bu<sub>3</sub>P)<sub>2</sub>. In the oxidative addition step in Scheme 3, *Pd must not only act like singlet carbene to generate π-complexes for binding, it must also interact with the proximal C–X bond with either retention or inversion, presumably in concerted manners, for which the σ-bond version of the synergistic bonding may be envisioned (Scheme 4). For such processes of low activation barriers, an “effective” 14-electron species may be considered to be critically desired. Although the transmetalation step in Scheme 3 is not at all limited to transition metals, the reductive elimination step, for which a concerted microscopic reversal of oxidative addition discussed above appears to be a reasonable and useful working hypothesis, must once again rely on the “super-carbenoidal” transition metals to complete a redox catalyst cycle. Of course, many variants of the mechanism shown in Scheme 3 are conceivable, and they may be useful in dealing with some finer details.*

## ALKYNE ELEMENTOMETALATION–PD-CATALYZED CROSS-COUPLING ROUTES TO ALKENES

**Historical background of alkene syntheses.** Before the advent of Pd-catalyzed alkenylation<sup>15,45</sup> and alkynylation<sup>35</sup> in the 1970s, syntheses of regio- and stereodefined alkenes had been mostly achieved by (a) carbonyl olefination, which must proceed via addition–elimination processes such as the Wittig reaction<sup>46</sup> and its variants, the Horner-Wadsworth-Emmons reaction<sup>47</sup> and its later modifications including *Z*-selective Still-Gennari<sup>48</sup> and Ando<sup>49</sup> versions as well as (b) Peterson olefination<sup>50</sup> and its variants including Corey-Schlessinger-Mills methacrylaldehyde synthesis,<sup>51</sup> and (c) Julia<sup>52</sup> and related olefination reactions. Even today, many of these reactions collectively represent the mainstay of alkene syntheses. From the viewpoint of alkene syntheses in the  $\gamma(es)^2$  manner, however, these conventional methods have been associated with various frustrating limitations to be overcome. With the exception of the alkyne addition routes, many of which can proceed in high ( $\geq 98\%$ ) stereoselectivity, most of the widely used conventional methods including all of the carbonyl olefination reactions mentioned above must involve  $\beta$ -elimination, which fundamentally lacks high ( $\geq 98\%$ ) stereoselectivity and often tends to be regiochemically capricious as well.

As discussed earlier, Pd-catalyzed alkenylation is thought to proceed generally via reductive elimination, although some involving the use of relatively non-polar C–M bonds such as C–B, C–Si, and C–Sn are known to proceed at least partially via carbometalation– $\beta$ -elimination. In sharp contrast with  $\beta$ -elimination, reductive elimination, which is predominantly a  $\sigma$ -bond process, can proceed in most cases with full retention of all alkenyl structural details. Moreover, the scope of Pd-catalyzed alkenylation is fundamentally limited only by the availability of the required alkenyl precursors, as either  $R^1M$  or  $R^2X$ , and a wide range of methods for their preparation, both known and yet to be developed, may be considered and utilized. As discussed in detail, many of the Pd-catalyzed alkenylation reactions have displayed highly favorable results as judged by the  $\gamma(\text{es})^2$  criteria. Thus, Pd-catalyzed alkenylation has evolved since the mid-1970s into arguably the most general and highly selective ( $\geq 98\%$ ) method of alkene synthesis known to date.

At this point, it is both useful and important to classify the alkenyl groups,  $R^1$  and/or  $R^2$  in  $R^1M$  and/or  $R^2X$ , into the following ten structural types (Table 4). Since our attention is mainly focused on those cases where both regio- and stereochemical details critically matter, no intentional discussion of Type I and II alkenyl groups is presented.

Type	Alkenyl Descriptor	Structure	Regiodefined?	Stereodefined?
I	Vinyl	$\text{H}_2\text{C}=\text{CH}-$	No	No
II	$\alpha$ -Monosubstituted	$\text{H}_2\text{C}=\overset{\text{R}}{\text{C}}-$	Yes	No
III	( <i>E</i> )- $\beta$ -Monosubstituted		Yes	Yes
IV	( <i>Z</i> )- $\beta$ -Monosubstituted		Yes	Yes
V	$\alpha, \beta$ - <i>cis</i> -Disubstituted		Yes	Yes
VI	$\alpha, \beta$ - <i>trans</i> -Disubstituted		Yes	Yes
VII	( <i>E</i> )- $\beta, \beta'$ -Disubstituted <sup>a</sup>		Yes	Yes
VIII	( <i>Z</i> )- $\beta, \beta'$ -Disubstituted <sup>a</sup>		Yes	Yes
IX	( <i>E</i> )- $\alpha, \beta, \beta'$ -Trisubstituted <sup>a</sup>		Yes	Yes
X	( <i>Z</i> )- $\alpha, \beta, \beta'$ -Trisubstituted <sup>a</sup>		Yes	Yes

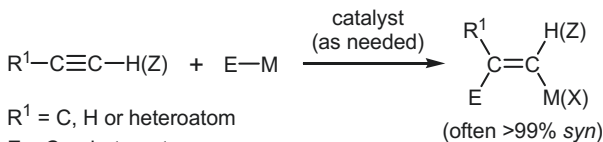
<sup>a</sup>  $R^L$  takes a higher priority than  $R^S$  according to the Cahn-Ingold-Prelog rule.

Table 4. Classification and Definition of Ten Types of Alkenyl Groups.

## ELEMENTOMETALATION

Addition of element–metal bonds (E–M), where E is H, C, a heteroatom (X), or a metal (M'), to alkynes and alkenes may be collectively termed *elementometalation*. As long as M is coordinatively unsaturated, providing one or more valence shell empty orbitals, *syn*-elementometalation should, in principle, be feasible and facile, as suggested by the synergistic bonding scheme involving the bonding and antibonding orbitals of an E–M bond as a HOMO and LUMO pair for interacting with a  $\pi^*$ - and  $\pi$ -orbital pair of alkynes and alkenes, as shown in Scheme 5 for hydrometalation, carbometalation, “heterometalation”, and metallometalation. As such, these processes are stoichiometric, and the metals (M and M') must be reasonably inexpensive. Besides this practically important factor, there are other chemical factors limiting the available choices of M. Thus, the generally high lattice energies of hydrides and other EM's of alkali metals and alkaline earth metals make it difficult to observe their favorable elementometalation reactions. In reality, B and Al are just about the only two reasonably inexpensive and non-toxic main group metals capable of readily participating in highly satisfactory uncatalyzed elementometalation reactions. Among *d*-block transition metals, Zr and Cu readily participate in stoichiometric *syn*-elementometalation reactions and nicely complement B and Al. For cost reasons, Ti, Mn, and Fe are also attractive, but their elementometalation reactions need further explorations. Likewise, transition metal-catalyzed elementometalation reactions of Si, Ge, and Sn are promising,<sup>53</sup> but their adoption will have to be fully justified through objective overall comparisons with B, Al, Zr, and Cu. In this article, no specific discussion of alkyne metallometalation is intended.

*Plausible concerted mechanism for syn-elementometalation*

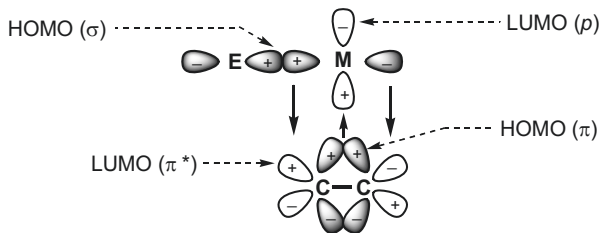


$R^1 = C, H$  or heteroatom

$Z = C$  or heteroatom

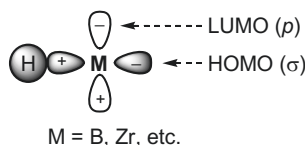
$E = H, C, X$  (nonmetallic heteroatom), or  $M'$  (metal)

*Synergistic HOMO-LUMO interaction schemes for elementometalation*

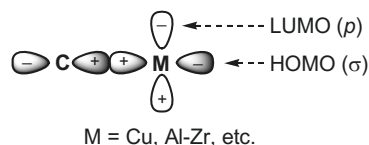


*Structures of various addends*

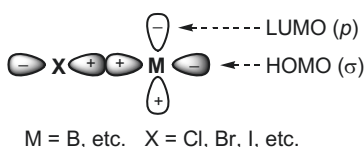
**Hydrometalation**



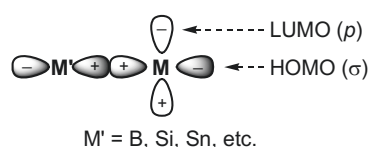
**Carbometalation**



**Heterometalation**



**Metallometalation**



*Scheme 5.*

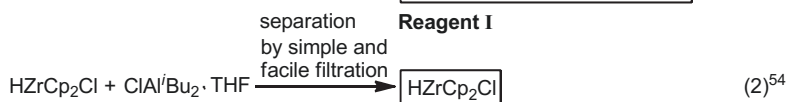
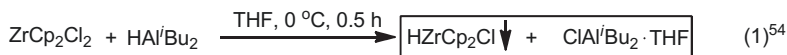
Importantly, the four metals mentioned above are mutually more complementary than competitive. As summarized briefly in Table 5, hydroboration is the broadest in scope and the most highly chemoselective in the “conventional” sense among all currently known alkyne hydrometalation reactions. Although somewhat more limited in scope and chemoselectivity, Zr tends to display the highest regioselectivity. More significantly, its reactivity in the subsequent Pd-catalyzed cross-coupling is considerably higher than that of B. In many cases where Zr works well, it therefore tends to be the metal of choice. Overall, B and Zr are the two best choices for hydrometalation. Difficulties associated with the relatively high cost of commercially available  $HZrCp_2Cl$  and its relatively short shelf-life have been finally resolved by the develop-

ment of an operationally simple, economical, clean, and satisfactory reaction of  $\text{ZrCp}_2\text{Cl}_2$  with one equivalent of  $^i\text{Bu}_2\text{AlH}$  in THF for generating genuine  $\text{HZrCp}_2\text{Cl}$  (Scheme 6).<sup>54</sup>

syn-Elementometalation	B	Zr	Al	Cu
syn-Hydrometalation (Types III-VI)	<ul style="list-style-type: none"> <li>Widest scope and applicability.</li> <li>Most tolerant of carbonyl and other heterofunctional groups.</li> <li>Relatively slow in Pd-cat. cross-coupling.</li> <li>Prone to <math>\pi</math>-addition-elimination leading to regio- and stereo-scrambling.</li> <li>Recent cross-coupling procedures increasingly satisfactory.</li> </ul>	<ul style="list-style-type: none"> <li>Reasonable scope.</li> <li>Highly regioselective with <math>\text{R}^1\text{—C}\equiv\text{C—H}</math>, esp. with conjugated terminal enynes and some internal alkynes, etc.</li> <li>Recent preparative procedure of <math>\text{HZrCp}_2\text{Cl}</math> very convenient.</li> <li>Highest reactivity in Pd-cat. cross-coupling among the four metals listed.</li> </ul>	<ul style="list-style-type: none"> <li>More limited than B or Zr.</li> <li>Alkynyl H or halogen abstraction problematic.</li> </ul>	<ul style="list-style-type: none"> <li>Relatively little developed.</li> </ul>
syn-Carbometalation (Types VII&VIII)	<ul style="list-style-type: none"> <li>Uncatalyzed four-centered carboboration essentially unknown.</li> </ul>	<ul style="list-style-type: none"> <li>Zr alone tends to undergo cyclic carbocationation, but it is a good metal as catalyst for carboulumination.</li> </ul>	<ul style="list-style-type: none"> <li>Zr-cat. methylalumination (ZMA) is of broad scope with respect to <math>\text{R}^1</math> of <math>\text{R}^1\text{—C}\equiv\text{C—H}</math> and of very high synthetic value.</li> <li>Some benzyl, allyl, and higher <i>n</i>-alkylaluminums also react readily, but selectivity problematical.</li> <li>&gt;150 complex natural products prepared.</li> <li>Al used together with Zn in some cases is very satisfactory in Pd-cat. cross-coupling.</li> </ul>	<ul style="list-style-type: none"> <li>Primary alkyl-cupration useful.</li> <li>Types VII and VIII as well as IV alkenyl derivatives accessible.</li> <li>Methylcupration sluggish. Use ZMA instead.</li> <li>Cu-Zn combination very good in Pd-cat. cross-coupling.</li> </ul>
syn-Halometalation (Types VII&VIII)	<ul style="list-style-type: none"> <li>Bromoboration of alkynes facile and broadly applicable.</li> <li>A wide range of Type VII and VIII alkenyl derivatives are accessible.</li> <li>With ethyne Type III alkenyl derivatives are accessible, but its use needs justification.</li> <li>Recent procedures for both bromoboration and subsequent Pd-cat. cross-coupling very promising (see Scheme 9).</li> </ul>	<ul style="list-style-type: none"> <li>Appears to be unknown.</li> </ul>	<ul style="list-style-type: none"> <li>Appears to be unknown.</li> </ul>	<ul style="list-style-type: none"> <li>Appears to be unknown.</li> </ul>

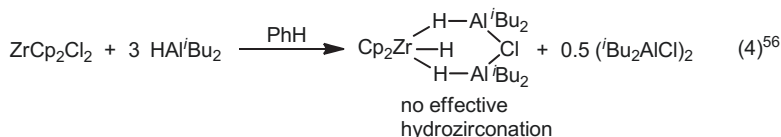
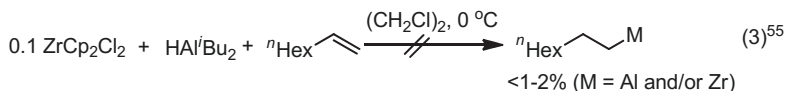
Table 5. Current Profiles of Hydro-, Carbo-, and Halometalation Reactions with B, Zr, Al, and Cu.



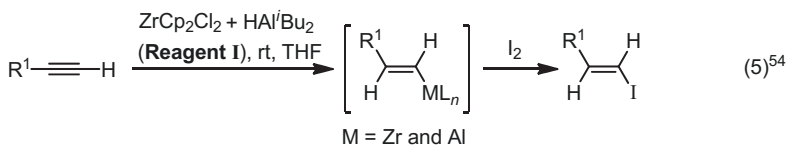


**Reagent I**  
**Reagent II** (generated and used *in situ*)  
**Reagent III** (isolated and stored)

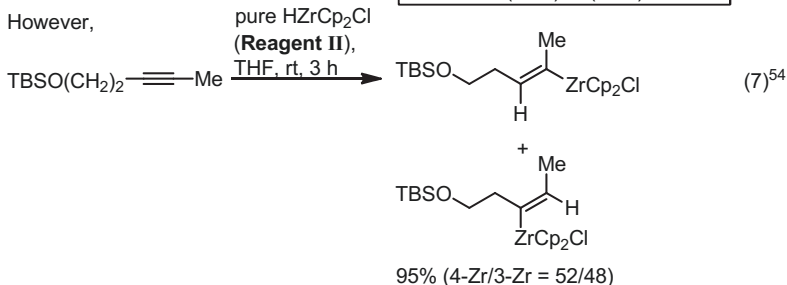
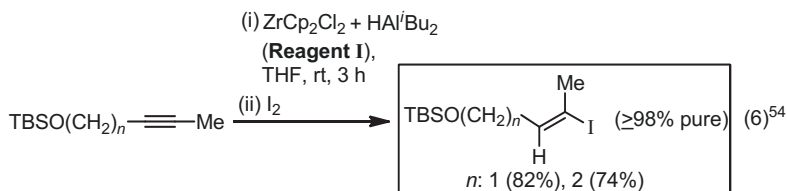
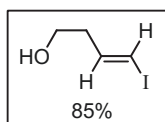
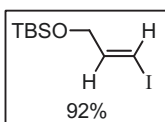
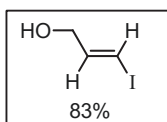
Previously reported results



Hydrozirconation-Iodinolysis



R: <sup>n</sup>Hex (91%), HOCH<sub>2</sub> (83%),<sup>a</sup> TBSOCH<sub>2</sub> (92%), HO(CH<sub>2</sub>)<sub>2</sub> (85%),<sup>a</sup>  
TBSOCH(<sup>n</sup>Pr) (93%), TBSOCH<sub>2</sub>CHMe (90%), PhMe<sub>2</sub>Si (81%),  
(*E*)-<sup>n</sup>HexCH=CH (95%), (*E*)-TBSO- (87%)



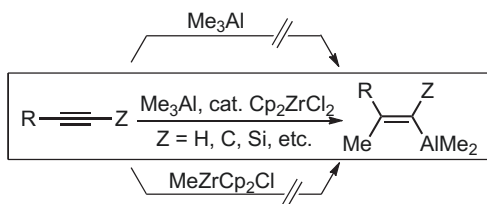
<sup>a</sup> Additional one equivalent HAl<sup>i</sup>Bu<sub>2</sub> was used to metalate OH group.

Scheme 6.

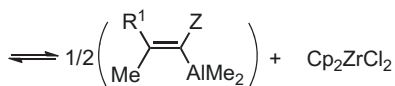
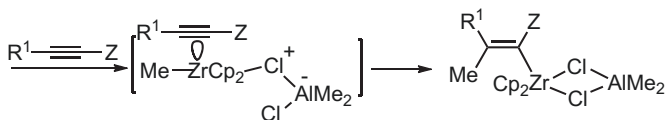
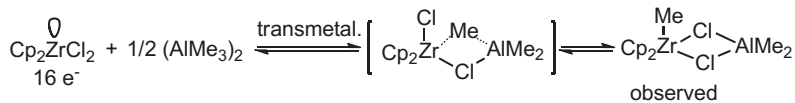
In marked contrast, direct and uncatalyzed four-centered carboboration is still essentially unknown. This may tentatively be attributed to the very short, sterically hindered C–B bond. Currently, alkylcoppers<sup>57</sup> appear to be the only class of organometals that undergo satisfactory uncatalyzed, stoichiometric, and controlled single-stage carbometalation with alkynes. Although trialkylaluminums do react with terminal alkynes at elevated temperatures, it is complicated by terminal alumination.<sup>58</sup> This difficulty was overcome for the single most important case of alkyne methylalumination through the discovery and development of the Zr-catalyzed methylalumination of alkynes with Me<sub>3</sub>Al (ZMA reaction).<sup>26a,59,60</sup> Ethyl- and higher alkylaluminums<sup>60,61</sup> as well as those containing allyl and benzyl groups<sup>62</sup> react readily but display disappointingly low regioselectivity ranges due mainly to intervention of cyclic carbozirconation,<sup>61</sup> which must be further improved.

Despite such limitations the ZMA reaction has proved to be highly useful because of the special significance of methyl-branched *E*-trisubstituted alkenes as a widely occurring structural unit in many isoprenoids. Detailed mechanistic studies have established that it involves an Al-promoted *syn*-carbozirconation of alkynes, as depicted in Scheme 7. In the interaction with alkynes, the active Zr–Al species must act as a “super-acidic” methylzirconium reagent through its interaction with an alane, i.e., operation of the “two-is-better-than-one” principle.<sup>63</sup> (*E*)-β, β-Disubstituted trisubstituted (Type VIII) alkenylaluminum derivatives thus generated can be *in situ* converted to a wide range of the corresponding trisubstituted alkenes, as summarized in Scheme 7.

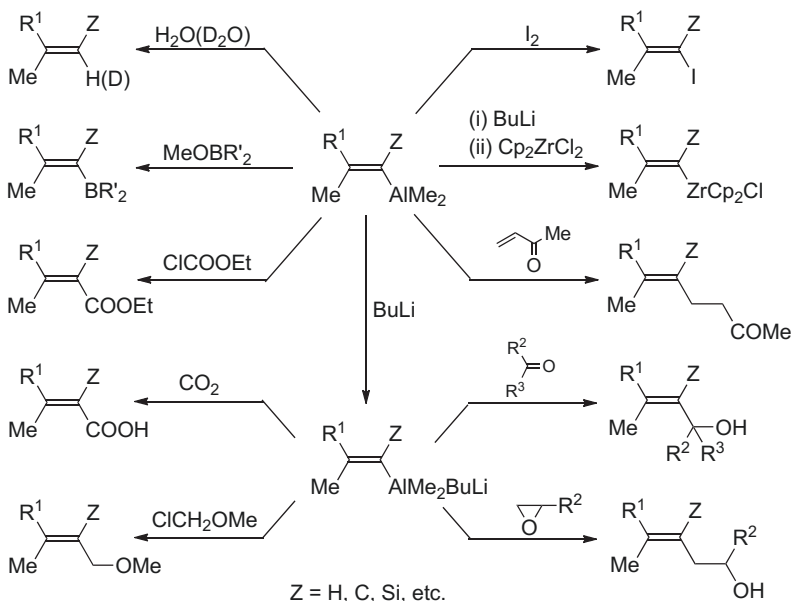
Zr-catalyzed methylalumination of alkynes (ZMA)<sup>59</sup>



proposed mechanism<sup>60</sup>



Z = H, C, Si, etc.



Scheme 7.

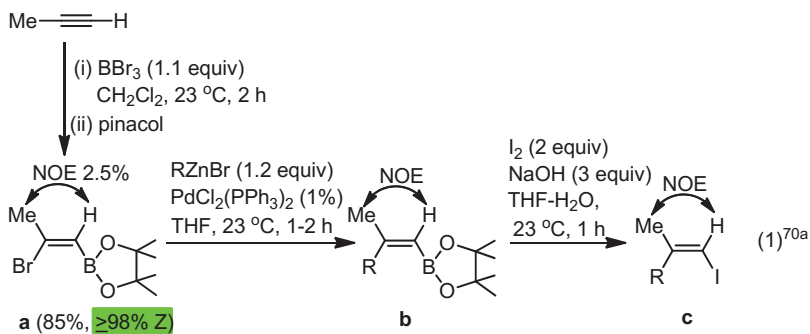
For selective syntheses of (*Z*)- $\beta,\beta$ -disubstituted Type VIII alkenyl derivatives, alkyne haloboration reactions discovered by Lappert<sup>64</sup> in the early 1960s and developed by Suzuki<sup>65</sup> in the 1980s are of considerable interest. In particular, the alkyne bromoboration–Negishi coupling tandem process<sup>66</sup> promised to provide a broadly applicable method for the head-to-tail (**H-to-T**) construction of various types of trisubstituted alkenes (Scheme 8). In reality, however, there were a number of undesirable limitations, of which the following were some of the most critical:

- i. formation of (*E*)- $\beta$ -haloethenylboranes through essentially full stereoisomerization,<sup>67</sup>
- ii. partial stereoisomerization ( $\geq 10\%$ ) in the arguably single-most important case of propyne haloboration,<sup>68</sup>
- iii. competitive and extensive  $\beta$ -dehaloboration to give the starting alkynes in cases where 1-alkynes contain unsaturated aryl, alkenyl, and alkynyl groups.
- iv. sluggish second Pd-catalyzed cross-coupling reactions under the reported Suzuki coupling conditions.<sup>66</sup> To avoid this difficulty, use of the second Negishi coupling via  $B\rightarrow I^{69-71}$  and even  $B\rightarrow I\rightarrow Li^{71}$  transformations have been reported as more satisfactory, if circuitous, alternatives.

Although no investigation of the item (i) has been attempted, highly satisfactory procedures have been developed for fully avoiding the difficulty described in the item (ii)<sup>70a</sup> (Eq. 1, Scheme 8) and substantially improving the second-stage Pd-catalyzed cross-coupling by the direct use of alkenylborane intermediates<sup>72</sup> (Eq. 2, Scheme 8). Additionally, a major step towards establishment of highly general and satisfactory alkene synthetic methods based on elementometalation–Pd-catalyzed cross-coupling has been taken with recent development of the hitherto unknown arylethyne bromoboration–Pd-catalyzed cross-coupling tandem process<sup>71b</sup> (Eqs. 4–7, Scheme 8). At present, however, use of conjugated enynes and diynes in place of arylethyne appears to be even more challenging than the cases of arylethyne, and it is currently under investigation.

Even at the current stage, the alkyne elementometalation–Pd-catalyzed cross-coupling tandem processes summarized in Table 5 provide collectively by far the most widely applicable and satisfactory routes to various types of acyclic alkenes.

Propyne bromoboration–Negishi coupling route to Type VIII alkenyl derivatives

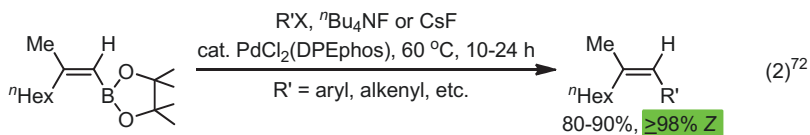


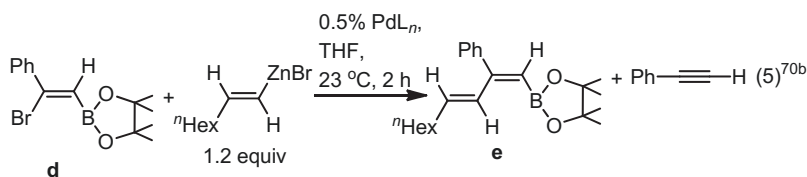
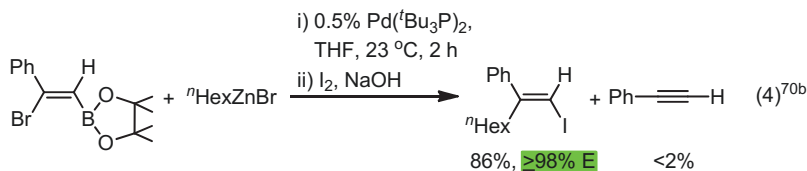
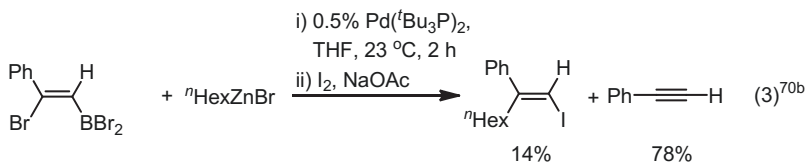
Note:  $\text{Me}(\text{Br})\text{C}=\text{CHBBr}_2$  was not isolated and therefore is not shown.

R	Yield (%) <sup>a</sup>		R	Yield (%) <sup>a</sup>	
	<b>b</b>	<b>c</b>		<b>b</b>	<b>c</b>
<sup>n</sup> Hex	87	86	( <i>E</i> )- <sup>n</sup> HexCH=CH	96	– <sup>b</sup>
<sup>t</sup> Bu	86	82	( <i>E</i> )- <sup>n</sup> Hex(Me)C=CH	83	81
<sup>c</sup> Hex	84	88	( <i>E</i> )-HOCH <sub>2</sub> CH=CH	– <sup>c</sup>	77 <sup>d</sup>
Me <sub>2</sub> C=CHCH <sub>2</sub>	79	84	( <i>E</i> )-TBSOCH <sub>2</sub> C=CH	90	84
PhCH <sub>2</sub>	83	81	Ph	86	86
Me <sub>2</sub> C=CCH <sub>2</sub> CH <sub>2</sub>	73	87	4-MeOC <sub>6</sub> H <sub>4</sub>	87	89
PhCH <sub>2</sub> CH <sub>2</sub>	76	80	4-ClC <sub>6</sub> H <sub>4</sub>	85	85
<sup>n</sup> HexC≡CCH <sub>2</sub> CH <sub>2</sub>	79	90	<sup>n</sup> BuC≡C	83	87
CH <sub>2</sub> =CH	82	84	TBSC≡C	90 <sup>e</sup>	88

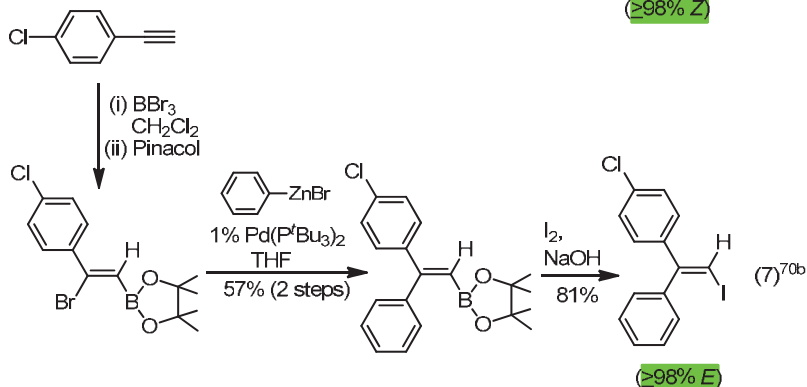
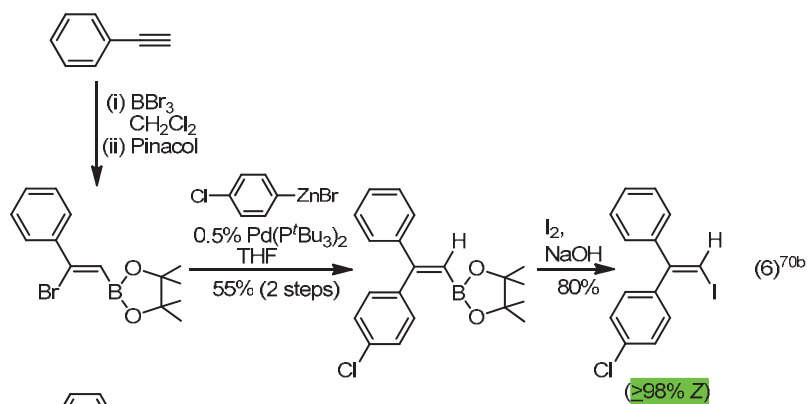
<sup>a</sup> Isolated yields of **b** and **c** are based on **a**.

<sup>c</sup> Not isolated. <sup>b</sup> Not prepared. <sup>d</sup> Based on  $\text{MeC}\equiv\text{CH}$  and  $\text{HOCH}_2\text{C}\equiv\text{CH}$ .





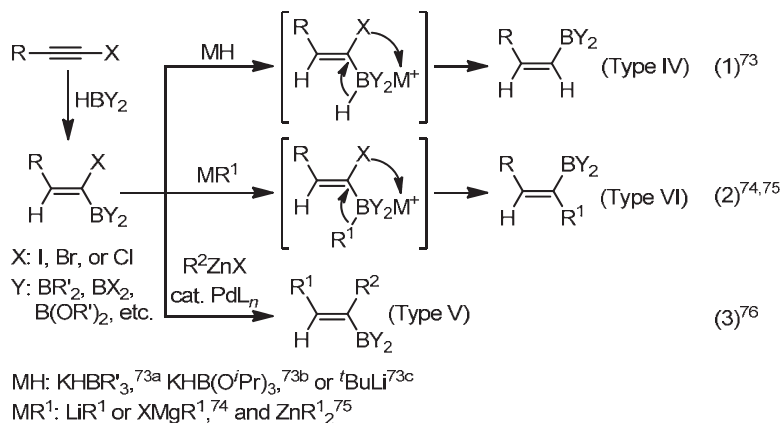
PdL <sub>n</sub> (0.5 mol %)	e (%)	Ph-C≡CH (%)	d (%)
Pd(tBu <sub>3</sub> P) <sub>2</sub>	77	<2	<2
PEPPSI	77	<2	<2
Pd(DPEphos)Cl <sub>2</sub>	<2	20	67
Pd(dppf)Cl <sub>2</sub>	<2	22	52
PdCl <sub>2</sub>	38	15	35



Scheme 8.

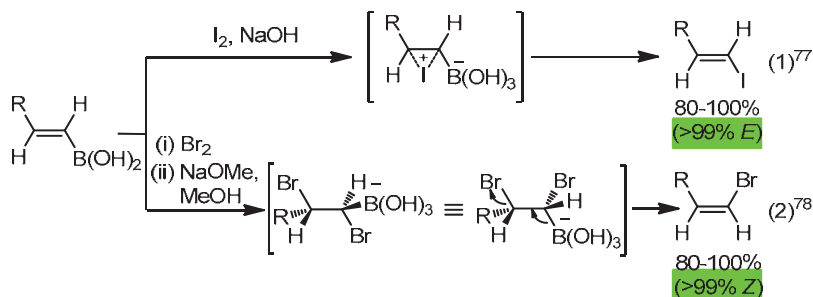
ALKYNE SYN-ELEMENTOMETALATION FOLLOWED BY STEREO- AND/OR REGIOISOMERIZATION

(a) ***syn*-Hydroboration of 1-halo-1-alkynes.** *syn*-Hydroboration of internal alkynes tends to give a mixture of two possible regioisomers. In cases where 1-halo-1-alkynes are used as internal alkynes, however the reaction is nearly 100% regioselective, placing B at the halogen-bound carbon. The resultant (*Z*)- $\alpha$ -haloalkenylboranes can be used to prepare (i) (*Z*)-1-alkenylboranes (Type IV),<sup>73</sup> (ii) (*Z*)- $\alpha,\beta$ -disubstituted alkenylboranes (Type V),<sup>76</sup> and (iii) (*E*)- $\alpha,\beta$ -disubstituted alkenylboranes (Type VI),<sup>74,75</sup> as summarized in Scheme 9.



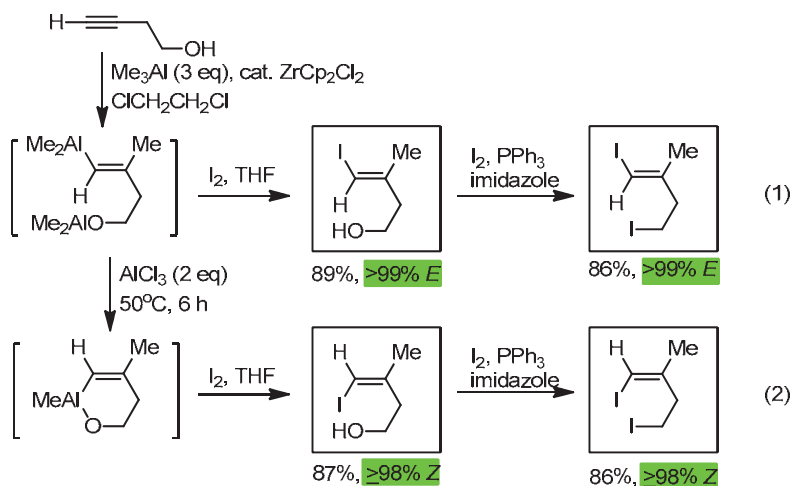
Scheme 9.

(b) ***syn*-Hydroboration of 1-alkynes followed by halogenolysis with either retention or inversion.** Hydroboration of 1-alkynes followed by iodinolysis proceeds with retention to give (*E*)-1-iodoalkenes (Type III) of >99% purity,<sup>77</sup> whereas the corresponding brominolysis in the presence of NaOMe in MeOH produces the stereoinverted *Z*-isomer (Type IV) of >99% purity<sup>78</sup> (Scheme 10).



Scheme 10.

(c) ***syn*-Zr-catalyzed carboalumination (ZMA) of proximally heterofunctional alkynes followed by stereoisomerization.** The ZMA reaction of homopropargyl alcohol followed by treatment with  $\text{AlCl}_3$  at  $50^\circ\text{C}$  for several hours provides the corresponding *Z* isomer.<sup>79,80</sup> Its mono- and diiodo derivatives have proven to be useful Type VIII alkenyl reagents for the synthesis of a variety of *Z*-alkene-containing terpenoids, as discussed later in detail (Scheme 11).



Scheme 11.

## MAGICAL POWER OF TRANSITION METALS: PRESENT AND FUTURE OUTLOOK

As a LEGO-game like tool for synthesizing all conceivable types of organic compounds, the Pd-catalyzed cross-coupling between  $\text{R}^1\text{M}$  ( $\text{M} = \text{Zn}, \text{Al}, \text{B}, \text{Zr}$ , etc.) and  $\text{R}^2\text{X}$  ( $\text{X} = \text{halogens}$ , etc.) for producing  $\text{R}^1\text{-R}^2$  as organic products has emerged as the currently most widely applicable and satisfactory method in the  $\gamma(\text{es})^2$  manner. A glance at Table 3 might give us an impression that our task in the “LEGO-game” might be a little more than halfway complete, provided that both  $\text{R}^1\text{M}$  and  $\text{R}^2\text{X}$  are available in the desirable forms. At present, one may state that the overall scope of the syntheses of  $\text{R}^1\text{-R}^2$  is limited more by the availability of appropriately structured  $\text{R}^1\text{M}$  and  $\text{R}^2\text{X}$ . One of the most challenging aspects of organic syntheses is to be able to synthesize not only all conceivable types of monoenes shown in Table 4, for which various types of alkyne elementometalation reactions (Schemes 5–11 and Table 5) are indispensable, but also any of their desired combinations, such as all conceivable types of di-, tri- and higher oligoenes, and so on. Although no details are presented here, it is gratifying that, through the use of various combinations of alkyne elementometalation reactions and the Pd-catalyzed



alkenyl–alkenyl cross-coupling procedures, mostly Negishi which is supplemented with Suzuki, we have just synthesized four possible types of conjugated dienes and eight possible types of conjugated trienes in high overall yields and in  $\geq 98\%$  stereoselectivities throughout the syntheses, in other words, without generating detectable amounts of any stereoisomers.<sup>37a</sup>

Although there are some pending issues, such as alkynyl–alkynyl cross-coupling that is prone to produce mixtures of all three possible conjugated diynes ( $R^1C\equiv CC\equiv CR^2$ ,  $R^1C\equiv CC\equiv CR^1$ , and  $R^2C\equiv CC\equiv CR^2$ ), the Pd-catalyzed cross-coupling reactions between two unsaturated carbon groups, i.e., aryl, alkenyl, and alkynyl groups are generally well-behaved (Table 3). Even in the cases of conjugated diyne syntheses, indirect but efficient and selective routes are available.<sup>19b,81</sup>

As we turn our attention to the Pd-catalyzed cross-coupling involving alkylmetals and/or alkyl electrophiles including allyl, benzyl, propargyl, and their higher homologues, it is readily noted from Table 3 that the use of alkyl electrophiles lacking proximal  $\pi$ -bonds is considerably more challenging, although some notable progress has been made in recent years. On the other hand, alkylmetals and proximally  $\pi$ -bonded alkyl electrophiles display sufficiently high reactivities, as illustrated for the cases of allylic electrophiles (Scheme 4). Clearly, this is one large area of Pd-catalyzed cross-coupling corresponding to nearly 30 out of 72 cases of cross-coupling combinations shown in Table 3 requiring major attentions. As many of these cases are being further investigated, it should be clearly noted that the following satisfactory options do exist: (1) Those nine cases of cross-coupling involving two allyl, benzyl, and/or propargyl cross-coupling partners are at best capricious, but the same desired products may be obtained in the  $\gamma$ (es)<sup>2</sup> manner by shifting the point of C–C bond formation by one<sup>82,83</sup> (Table 3). (2) For alkyl–alkyl coupling without the involvement of proximal  $\pi$ -bonds, the reaction of alkyl Grignard reagents with alkyl halides and related electrophiles catalyzed with  $Li_2CuCl_4$  or other related Cu catalysts still appears to be the current best option.<sup>25</sup>

## ZIRCONIUM-CATALYZED ASYMMETRIC CARBOALUMINATION OF ALKENES (ZACA REACTION)

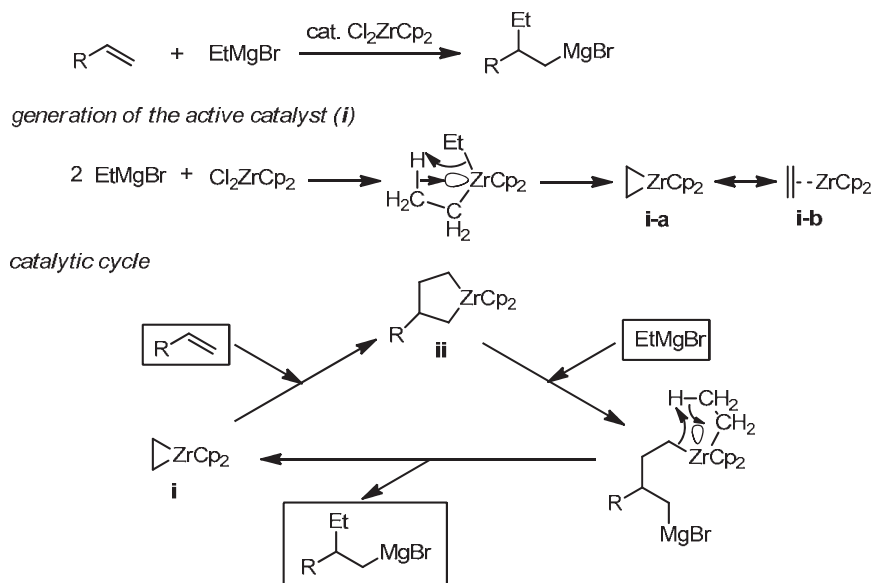
At the time we discovered the Zr-catalyzed carboalumination of alkynes (ZMA) in 1978 (Scheme 7),<sup>59</sup> a dreamy thought of expanding the scope of this reaction so as to embrace its alkene version for asymmetric C–C bond formation, which would amount to the single-step version of the Ziegler–Natta alkene polymerization captured my mind. However, this seemingly easy task proved to be quite challenging, and several intermittent attempts over seventeen years supported heavily by our ongoing systematic investigations of zirconocene chemistry were needed to finally discover in 1995 the Zirconium-catalyzed Asymmetric Carboalumination of Alkenes (ZACA reaction hereafter),<sup>84</sup> as detailed below.

### **Historical and mechanistic background of carbometalation of alkenes and**

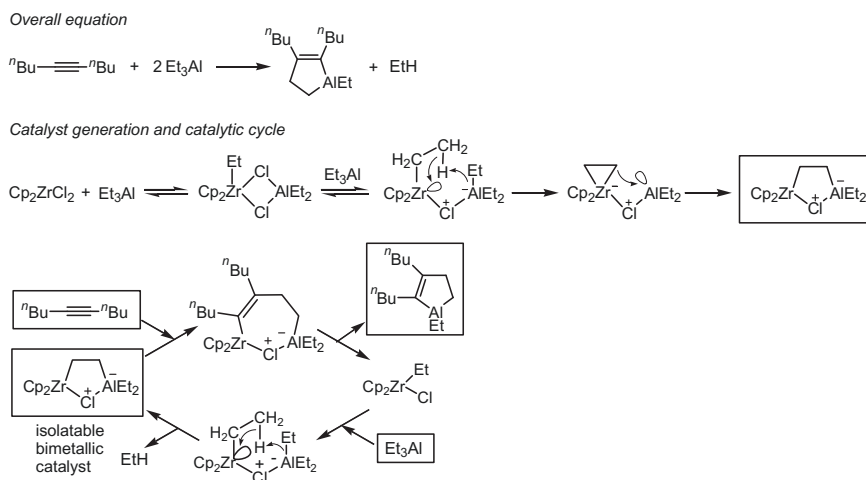
**alkynes with alkylzirconocenes derivatives.** The Zr-catalyzed methylalumination of alkynes (ZMA reaction) was shown to involve one-step *syn*-addition of a Me–Zr bond to 1-alkynes in an *anti*-Markovnikov manner followed by Zr-to-Al transmetalation on the resultant carbon group.<sup>60</sup> This reaction involves acyclic carbometalation of a “super-acidic”<sup>63,85</sup> Zr–Al bimetallic system (Scheme 7).

Several years later, Dzhemilev reported a seemingly analogous reaction of Zr-catalyzed carbomagnesiation of alkenes with EtMgBr (Scheme 12).<sup>86</sup> There did not appear any compelling reasons to suspect that the mechanisms of these two closely analogous reactions should be radically different. Through our systematic investigations of the “ZrCp<sub>2</sub>” chemistry,<sup>87</sup> however, we accidentally clarified that the Dzhemilev ethylmagnesiation of alkenes actually proceeded via a highly intricate series of transformations via (i) formation of Et<sub>2</sub>ZrCp<sub>2</sub>, (ii) β-agostic interaction-induced intramolecular “acid-base” interaction producing a zirconacyclopropane (**i-a**) which may also be viewed as a zirconocene-ethylene π-complex (**i-b**), (iii) cyclic carbozirconation of an alkene with **i** to give, typically a 3-substituted zirconacyclopentane (**ii**), (iv) subsequent reaction of **ii** with another molecule of EtMgBr leading to β-agostic interaction-induced “acid-base” interaction producing a 2-ethyl-1-alkylmagnesium bromide with regeneration of ethylene-ZrCp<sub>2</sub> π-complex (**i**). All of the steps proposed above have been independently and amply supported (Scheme 12).<sup>87,88</sup> We believe that both the discovery of the Dzhemilev ethylmagnesiation and our mechanistic clarification<sup>88</sup> have not only clearly established the existence of both acyclic and cyclic carbozirconation processes but also alerted us to sharply and carefully distinguish some seemingly analogous carbometalation reactions of zirconocene derivatives. We were later further surprised by the existence of bimetallic (involving both Zr and Al) cyclic carbozirconation of alkynes and alkenes that may be viewed as a hybrid of acyclic and cyclic carbozirconation<sup>61</sup> (Scheme 13). We also noted that our bimetallic (Zr–Al) cyclic carbozirconation process closely resembled the corresponding carbotitanation of alkenes with titanium-carbene species that can be viewed as a two-membered titanacycle (Tebbe reagent) generated from a Ti–Al bimetallic system.<sup>89</sup> Without going into detailed mechanistic discussions, the following brief summary may be presented: (i) Formation of metallacycles including metal-carbene complexes (two-membered metallacycles) is a widely observable phenomenon with coordinatively unsaturated organotransition metal complexes, especially in those cases where coordinatively unsaturated dialkylated organotransition metal species that are readily prone to β or even α-agostic interaction-induced cyclization are generated.<sup>90</sup> (ii) The propensity for generating the requisite “coordinatively unsaturated dialkyltransition metal species” rests on a delicate balance between the alkylating power of alkylmetal reagents, e.g., RLi > RMgX > RAlX<sub>2</sub>, and their ability to avoid formation of coordinatively saturated “ate” complexes. Thus, for example, trialkylalanes, e.g., Et<sub>3</sub>Al, do not dialkylate ZrCp<sub>2</sub>Cl<sub>2</sub> to give Et<sub>2</sub>ZrCp<sub>2</sub>. On the other hand, Grignard reagents, e.g., EtMgBr, readily dialkylate to give

a 16 e<sup>-</sup> Et<sub>2</sub>ZrCp<sub>2</sub>. Triethylation does proceed, but it is readily reversible. All these make alkylmagnesium derivatives some of the optimal reagents for converting ZrCp<sub>2</sub>Cl<sub>2</sub> into zirconacycles. (iii) Even with alkylalanes, however, zirconacycles may still be formed via “bimetallic intramolecular acid-base interaction” discussed above.

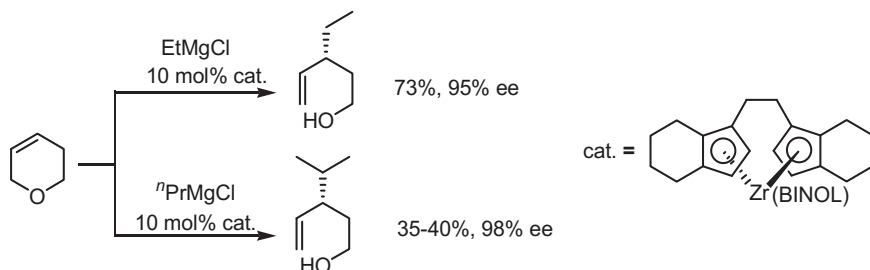


Scheme 12. Cyclic carbozirconation mechanism for Dzhemilev ethylmagnesiation.



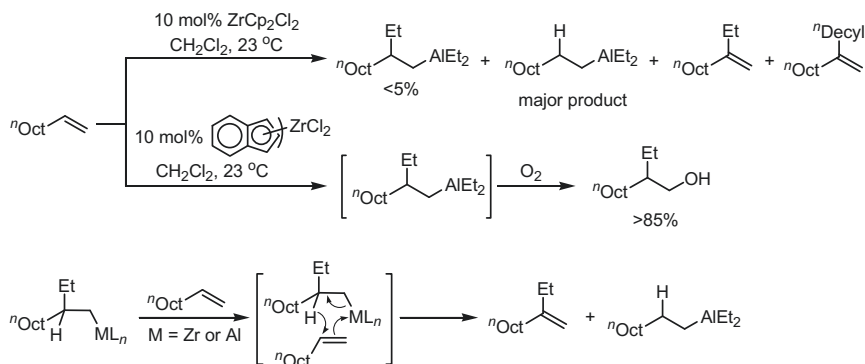
Scheme 13. Bimetallic cyclic carboalumination mechanism.<sup>61</sup>

**Catalytic asymmetric carbometalation of alkenes proceeding via Dzhemilev ethylmagnesiumiation.** The first catalytic and highly enantioselective alkene carbometalation with zirconocene derivatives was reported by Hoveyda in 1993.<sup>91</sup> Highly satisfactory results have been obtained through the use of Dzhemilev ethylmagnesiumiation of allyl ethers and allylamines (Scheme 14). Similar developments were also made later.<sup>92</sup>



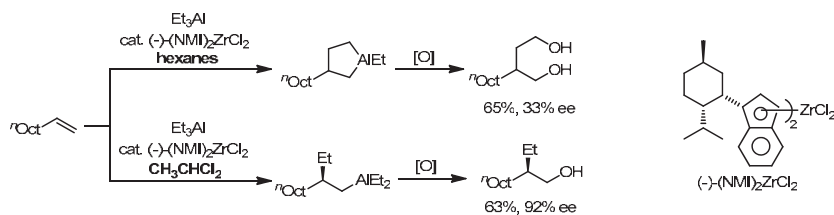
Scheme 14. Catalytic asymmetric carbometalation-elimination of allyl ethers with ethylmagnesium and chiral zirconocene derivatives.

Although the enantioselectivity in some cases is spectacularly high, a few critical limitations should be noted. As might be expected from mechanistic details of Dzhemilev carbomagnesiumiation discussed above, introduction of the singularly important Me group is not readily feasible. While introduction of Et is satisfactory, that of *n*Pr and longer alkyl groups is accompanied by regioisomerization leading to the formation of unattractive product mixtures.<sup>91-93</sup> Clearly, new alternate reactions *not requiring zirconacycles* were needed, especially for the most highly desirable case of enantioselective methylmetalation. In the meantime, our own efforts toward this goal were miserably failing. We then noted that all of our very tentative feasibility investigations leading to negative results were conducted with the parent  $\text{ZrCp}_2\text{Cl}_2$ . We finally decided to commit ourselves to the following two studies: (1) detailed fact-finding investigation of the reaction of 1-decene with 10 mol% of  $\text{ZrCp}_2\text{Cl}_2$  in  $\text{CH}_2\text{Cl}_2$  and (2) search for satisfactory procedures based on (1). These studies immediately led to some most useful results shown in Scheme 15. With  $(\text{Me}_5\text{C}_5)_2\text{ZrCl}_2$ , no reaction was observed under the same conditions.<sup>84</sup> Clearly, zirconocene derivatives of sufficiently, but not excessively, bulky ligands to suppress unwanted side reactions, most notably  $\beta$ -H transfer hydrometalation, while promoting the desired carbometalation, were needed for realizing our goal.



Scheme 15. Reaction of 1-decene with  $\text{Et}_3\text{Al}$  in the presence of various zirconocene derivatives.

Yet another ambush we briefly encountered was the initially unexpected Al-Zr bimetallic cyclic carbometalation of alkenes. Before 1995, we believed that dialkylation of zirconocene derivatives would be mandatory for observing the formation of zirconacyclopropanes via  $\beta$ -agostic interaction-induced cyclization. We were, however, surprised to find out that the reaction of 1-decene with  $\text{Et}_3\text{Al}$  in the presence of  $(\text{NMI})_2\text{ZrCl}_2$ <sup>94a</sup> in hexanes would proceed by cyclic carbometalation<sup>84b</sup> (Scheme 16), even though there were ample indications that trialkylalanes do not lead to dialkylation of zirconocene derivatives. It was indeed this surprising finding that led to the clarification and establishment of the *bimetallic cyclic mechanism for carbozirconation* of alkynes mentioned earlier (Scheme 13).<sup>61</sup> Fortunately, we soon learned that the use of more polar solvents including  $\text{CH}_2\text{Cl}_2$ ,  $\text{CH}_3\text{CHCl}_2$ , and  $(\text{CH}_2\text{Cl})_2$  almost totally suppressed the undesired cyclic carbometalation process, thereby promoting formation of the desired products (Scheme 16).<sup>84</sup>

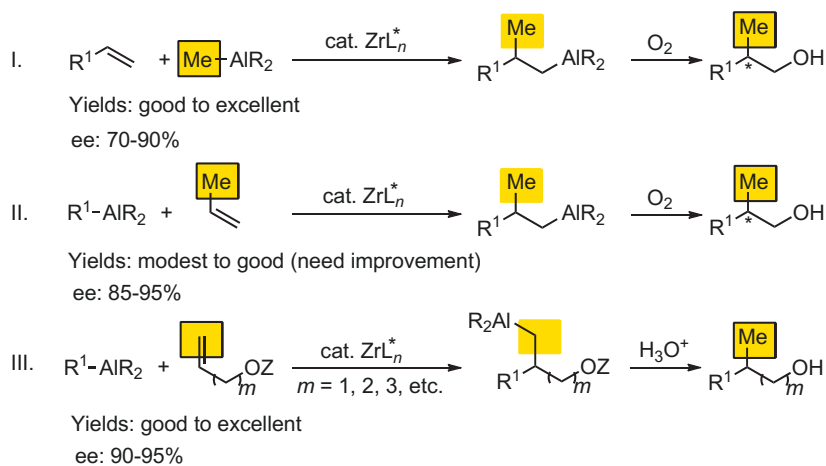


Scheme 16. Marked solvent effect in the reaction of 1-decene with  $\text{Et}_3\text{Al}$  in the presence of  $(\text{NMI})_2\text{ZrCl}_2$ .

Throughout our investigations, we were very much concerned about the third potential side reaction, i.e., Zr-catalyzed alkene polymerization of Ziegler and Natta.<sup>95</sup> However, this has hardly been of any serious concern.

In retrospect, this is not surprising, if one considers (i) essentially 1:1 alkene-to-alane ratios and (ii) absence of highly efficient polymerization promoters, such as methylaluminoxane (MAO), typically required in large quantities relative to trialkylalanes. In our ZACA reaction, the use of MAO and other promoters is not mandatory and typically not necessary, although addition of one equivalent or less of water or the corresponding amount of performed MAO can significantly promote otherwise slow ZACA reaction,<sup>96</sup> such as that of styrenes.

Having learned about three major pitfalls, namely (1) cyclic carbometalation, (2) H-transfer hydrometalation, and (3) Ziegler-Natta-type alkene polymerization as well as how to avoid them, our remaining major task was to find some satisfactory chiral zirconocene catalysts. In this respect, we have not yet made a systematic catalyst optimization involving catalyst designing. Instead, we have merely screened a dozen to fifteen known chiral zirconocene complexes. In our cases, widely used (ebi)ZrCl<sub>2</sub><sup>94b</sup> and its partially hydrogenated derivatives<sup>94c</sup> were less effective. The most effective among those tested thus far is Erker's (NMI)<sub>2</sub>ZrCl<sub>2</sub>.<sup>94a</sup> With either (*R*)- or (*S*)-isomer of commercially available (NMI)<sub>2</sub>ZrCl<sub>2</sub>,<sup>94d</sup> the approximate ranges of enantiomeric excesses observed in three mutually complementary ZACA reactions shown in Scheme 17 are 70–95% ee and the product yields are generally satisfactory, although there clearly exists room for improvement (Scheme 17).



Scheme 17. Three protocols for enantioselective synthesis of methyl-substituted 1-alkanols.

## CURRENT SUMMARY OF DEVELOPMENT AND APPLICATION OF ZACA REACTION AND CONCLUSION

Although no detailed discussion of applications of the ZACA reaction is intended here, the following favorable features of this novel asymmetric C–C bond formation reaction may be noted and exploited. In the interest

of providing a full list of the publications on ZACA reaction by the author's group, all original papers and pertinent reviews and so on are listed as references.<sup>63,69,75,84,87,97-120</sup>

1. The ZACA reaction is a novel and rare *catalytic asymmetric C–C bond formation reaction of terminal alkenes of one-point-binding without requiring any other functional groups*, even though various functional groups may be present.
2. There are *a few or possibly more alternate and mutually complementary procedures to choose from*, allowing highly flexible designs for the syntheses of chiral organic compounds<sup>98,100</sup> (Scheme 17).
3. In cases where ZACA products are obtained as *2-chirally branched 1-alcohols* via simple oxidation, typically with O<sub>2</sub>, of alanes, *lipase-catalyzed acetylation–ordinary column chromatography provides a widely applicable and convenient method of purification* by taking advantage of the sufficiently high ZACA-generated 70–95% enantiomeric excess levels of the crude products.<sup>106</sup>
4. In more demanding cases, *proximally ( $\gamma$  or  $\delta$ ) heterofunctional and hence readily purifiable 2-chiral 1-alcohols may be prepared first, purified, and further converted*.<sup>120</sup>
5. *In the syntheses of compounds with two or more chiral centers, the principle of statistical enantiomeric amplification is operative*. For the syntheses of deoxypolypropionates, for example, homologation by one 1,2-propylidene unit can be performed in one pot via ZACA–Pd-catalyzed vinylation tandem process.<sup>103</sup> At a realistic average enantioselectivity level of 80% ee, di, tri and tetrameric deoxypolypropionates are reliably predicted to be ca. 98, 99.9, and 99.99% ee, respectively.<sup>99,100</sup> *The only remaining task for preparing ultra-pure deoxypolypropionates is ordinary and very facile chromatographic purification of newly formed 2,4-dimethyl-1-hydroxybutyl moiety one at a time*.<sup>99-101,103,104</sup>

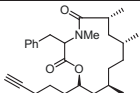
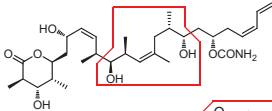
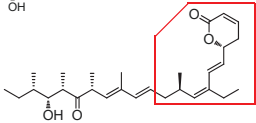
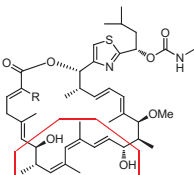
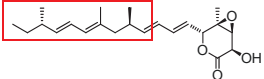
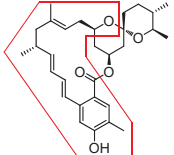
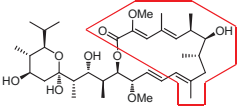
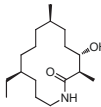
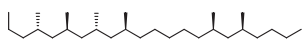
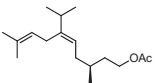
We believe that the ZACA reaction is a widely applicable, high-yielding, efficient and selective method for asymmetric C–C bond formation that is potentially economical. As of today, however, it has not yet been widely embraced by the organic synthetic community, although its application to natural products synthesis by other workers is known.<sup>96</sup> In the meantime, our own efforts to apply it to catalytic asymmetric syntheses of chiral natural products have been very enjoyable and most rewarding. In this review, only the names and structures of natural products and related compounds including about a dozen that have been totally synthesized through the use of ZACA reaction are presented in Table 6. It is indeed gratifying to note that *ZACA–Pd or Cu-catalyzed cross-coupling synergy does provide, in most cases, substantial improvements in efficiency and selectivity leading to significant increases in overall yields of pure desired compounds* over the previous syntheses of the same or related compounds. Coupled with various flexible options for purifying optically active products to ultra-high (>>99%) purity levels, its widespread application in the near future may be anticipated.

**Table 6.** Natural Products and Related Compounds of Biological and Medicinal Interest Synthesized via ZACA Reaction by the Authors's Group

entry	chiral compounds of biological and medicinal interest (year) <sup>ref</sup>	structure	total or fragment synthesis
(1)	vitamin E (2001 and 2002) <sup>97,98</sup>		total synthesis
(2)	vitamin K (2001) <sup>97,105</sup>		total synthesis
(3)	phytol (2001) <sup>97</sup>		total synthesis
(4)	scyphostatin (2004 and 2010) <sup>99,111</sup>		sidechain <sup>99</sup> and total synthesis <sup>111</sup>
(5)	TMC-151A-F C11-C20 fragment (2004) <sup>100</sup>		C11-C20 fragment
(6)	siphonarienal (2004) <sup>101</sup>		total synthesis
(7)	siphonarienone (2004) <sup>101</sup>		total synthesis
(8)	siphonarienolone (2004) <sup>101</sup>		total synthesis
(9)	(+)-sambutoxin C9-C18 fragment (2004) <sup>101</sup>		C9-C18 fragment
(10)	6,7-dehydrostipiamide (2004) <sup>102</sup>		total synthesis
(11)	ionomycin C1-C10 fragment (2005) <sup>103</sup>		C1-C10 fragment
(12)	borrelidin C3-C11 fragment (2005) <sup>103</sup>		C3-C11 fragment (Z = THP or TBDPS)
(13)	preen gland wax of the graylag goose, <i>Anser anser</i> (2006) <sup>104</sup>		total synthesis
(14)	doliculide C1-C9 fragment (2006) <sup>104</sup>		C1-C9 fragment
(15)	(+)-stellattamide A (2007) <sup>105</sup>		sidechain
(16)	(+)-stellattamide B (2007) <sup>105</sup>		C5-C11 sidechain



**Table 6.** (Continued.)

entry	chiral compounds of biological and medicinal interest (year) <sup>ref</sup>	structure	total or fragment synthesis
(17)	(-)-spongidepsin (2007) <sup>107</sup>		total synthesis
(18)	(+)-discodermolide (2007) <sup>75</sup>		C11-C17 fragment
(19)	(-)-callystatin A (2007) <sup>75</sup>		C1-C11 fragment
(20)	archazolides A and B (2007) <sup>75</sup> A: R = Me B: R = H		C7-C15 fragment
(21)	nafuredin (2008) <sup>108</sup>		C9-C18 fragment (formal total synthesis)
(22)	milbemycin $\beta_3$ (2008) <sup>108</sup>		C1-C13 fragment
(23)	bafilomycin A <sub>1</sub> (2008) <sup>108</sup>		C1-C11 fragment
(24)	fluvirucin A <sub>1</sub> (2008) <sup>109</sup>		total synthesis
(25)	4,6,8,10,16,18-hexamethyldocosane (2008) <sup>110</sup>		total synthesis
(26)	yellow scale pheromone (2008) <sup>69</sup>		total synthesis

*Table 6.* Natural Products and Related Compounds of Biological and Medical Interest Synthesized via ZACA Reaction by the Author's Group.

## FUTURE OUTLOOK

Aside from finer aspects of mechanisms, all of the *d*-block transition metal-catalyzed processes discussed above may be considered to proceed by two-electron transfer processes. As we pursue *d*-block transition metal-catalyzed processes involving photochemical and other related processes, their catalytic activities via one-electron transfer processes would seem to prove to be similarly important. From the abiological organic synthetic viewpoint, it still appears to be a largely unexplored field of vast potential.

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Portrait photo of Professor Negishi by photographer Ulla Montan.