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# Alkyne Elementometalation−Pd-Catalyzed Cross-Coupling. Toward Synthesis of All Conceivable Types of Acyclic Alkenes in High Yields, Efficiently, Selectively, Economically, and Safely: "Green" Way

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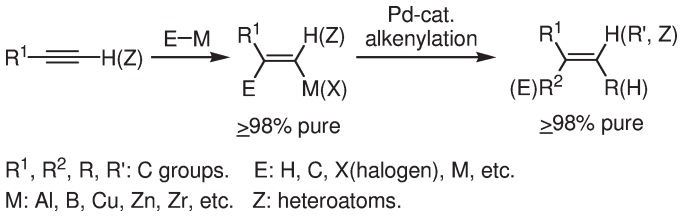
*Received February 19, 2010*




Palladium-catalyzed cross-coupling reactions, especially those involving Zn, Al, Zr (Negishi coupling), and B (Suzuki coupling), collectively have brought about "revolutionary" changes in organic synthesis. Thus, two regio- and stereodefined carbon groups generated as $R^1M$ (M = Zn, Al, B, Cu, Zr, etc.) and $R^2X$ (X = I, Br, OTs, etc.) may now be cross-coupled to give $R^1-R^2$ with essentially full retention of all structural features. For alkene syntheses, alkyne elementometalation reactions including hydrometalation (B, Al, Zr, etc.), carbometalation (Cu, Al−Zr, etc.), and haloboration ($BX_3$ where X is Cl, Br, and I) have proven to be critically important. Some representative examples of highly efficient and selective (≥98%) syntheses of di-, tri-, and oligoenes containing regio- and stereodefined di- and trisubstituted alkenes of all conceivable types will be discussed with emphasis on those of natural products. Some interesting but undesirable cases involving loss of the initial structural identities of the alkenyl groups are attributable to the formation of allylpalladium species, which must be either tamed or avoided. Some such examples involving the synthesis of 1,3-, 1,4-, and 1,5-dienes will also be discussed.

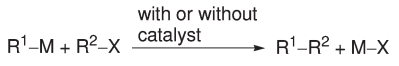
## Introduction

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 as 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 for preparing 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 more 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 "the last synthesis". (In this discussion, we do not at all intend to exclude non-natural organic compounds. However, the feasibility of synthesizing some non-natural molecules may not be unequivocally determined prior to their successful syntheses. Primarily for this reason, emphasis is placed on the syntheses of natural products which have already been synthesized at least by Nature.)

If one carefully goes over various aspects of the 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 would be "*to be able to*

DOI: 10.1021/jo1003218 Published on Web 05/14/2010

**SCHEME 1**




$R^1$, $R^2$: carbon groups. M: metal or metal-containing groups.
X: halogens or other leaving groups.

**TABLE 1. Scope and Limitations of Uncatalyzed Cross-Coupling with Grignard Reagents and Organoalkali Metals**[a]

| $R^1M$ \ $R^2X$ | ArX | X | X | X | Ar X | X | Alkyl X | RCOX |
|---|---|---|---|---|---|---|---|---|
| ArM | • These reactions do not proceed except in special cases | | | • Some work but they are of limited scope | | | Limited scope | Needs special procedures |
| M | | | | | | | | |
| M | | | | • Capricious and often nonselective<br>• Special Procedures are better but need much improvement | | | | |
| Ar M | | | | | | | | |
| M | | | | | | | | |
| Alkyl M | | | | • Some work but they are of limited scope | | | | |
| N≡C-M | | | | | | | | |
| C=C-OM | | | | | | | | |

[a]Note: Cu-promoted and Cu-catalyzed reactions have provided some satisfactory procedures. Conventional wisdom: Avoid cross-coupling! But, should we?

*synthesize any desired and fundamentally synthesizable organic compounds* (*a*) *in high* ***y****ields,* (*b*) ***e****fficiently* (*in as few steps as possible, for example*), (*c*) ***s****electively preferably all in* ≥*98*−*99% selectivity,* (*d*) ***e****conomically, and* (*e*) ***s****afely, abbreviated hereafter as the* ***y****(****es****)*$^2$ *manner.*"

As an argumentative but heavy-handed Ph.D. student at the University of Pennsylvania, the senior author of this paper was struck by a number of roundabout processes involved in well-known and important reactions, such as acetoacetic ester synthesis and malonic ester synthesis. "Why not devise more straightforward ways for the formation of all important C−C bonds?" This indeed was the starting point, if no more than a dream at that point, of his pursuit of C−C cross-coupling defined as shown in Scheme 1 and affectionately nicknamed *LEGO game approach to synthesis*. If any $R^1$ and $R^2$ groups, same or different, could be coupled in the y(es)$^2$ manner, most, if not all, of the synthetic tasks would be reduced to that of preparing fragmentary and simpler precursors $R^1M$ and $R^2X$. Moreover, this straightforward "retrosynthetic" fragmentation can be repeated as many times as needed.

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[1] (Table 1).

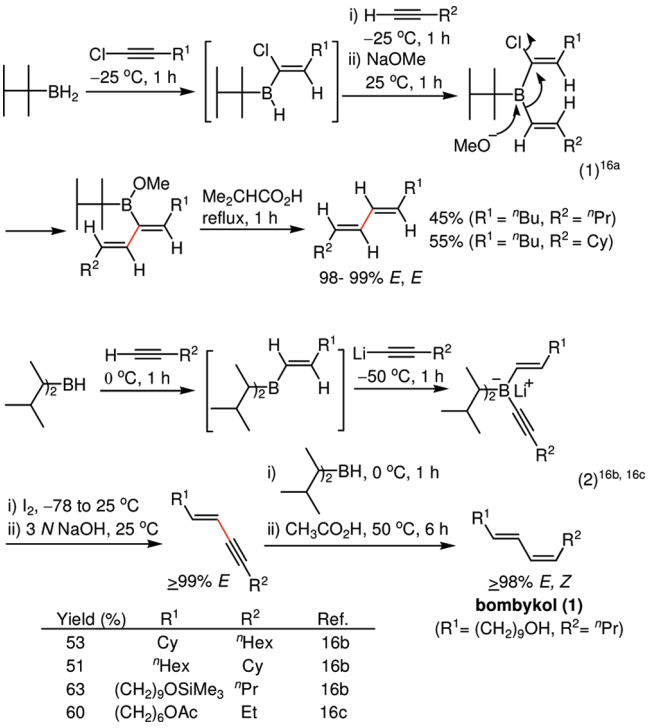
**Evolution of the Pd-Catalyzed Cross-Coupling.** The cross-coupling methodology has evolved mainly over the past four decades into one of the most widely applicable methods for C−C bond formation in the y(es)$^2$ manner, which is centered around the Pd-catalyzed cross-coupling with organometals containing Al, Zn, Zr (Negishi coupling),[2,3] B (Suzuki coupling),[2,4] and Sn (Stille coupling)[2,5] as well as those containing several other metals including Cu,[6] In,[7] Mg,[8] Mn,[9] and Si[10] (Hiyama coupling). Although of considerably more limited scope, both the seminal nature of the Ni-catalyzed Grignard cross-coupling of Tamao and Kumada[11a,b] as well as of Corriu[11c] 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.

In this paper, where alkenylation, briefly supplemented with alkynylation, is the main topic, attention will be mainly focused on the Pd-catalyzed version of the Negishi coupling and Suzuki coupling with those metals displaying superior features in their hydrometalation (B, Zr, and Al), carbometalation (Al and Zr), and halometalation (B), as well as Zn which generally offers the most favorable overall profile featuring (i) arguably the highest intrinsic reactivity under Pd-catalyzed conditions leading to generally high product yields, (ii) high turnover numbers (TONs hereafter) often exceeding a million,[12] (iii) nearly perfect (≥98%) retention of stereo- and regiochemical details in most cases, (iv) surprisingly favorable chemoselectivity, and (v) general absence of recognized inherent toxicity. It should be added that Zn salts can also serve as effective cocatalysts or promoters[13] accelerating other Pd-catalyzed cross-coupling reactions involving Al,[13] Zr,[13] B,[14] Cu,[6] Sn,[15] and so on.

Evolutions within the authors' group actually began with the development of some selective C−C bond formation reactions of alkenylboranes leading to most probably the earliest highly selective (≥98%) syntheses of unsymmetrically substituted conjugated (*E*,*E*)- and (*E*,*Z*)-dienes,[16] following the pioneering studies of alkyne hydroboration by Brown[17] and subsequent C−C bond formation by Zweifel[18] (Scheme 2).

Despite these successes, however, the authors' 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).[11] Our quixotic plans for substituting Grignard reagents with alkenylboranes and alkenylborates were uniformly unsuccessful.[19] 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 ≥99% *E* geometry.[19a] The corresponding Pd-catalyzed reactions were also observed, but no apparent advantage in the use of $Pd(PPh_3)_4$ in place of $Ni(PPh_3)_4$ was noticed. As can be surmised from our preceding studies shown in Scheme 2, one of our main goals was to be able to synthesize

**SCHEME 2**

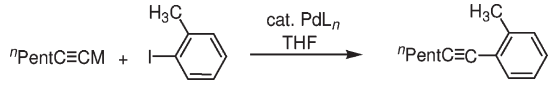



| Yield (%) | $R^1$ | $R^2$ | Ref. |
|---|---|---|---|
| 53 | Cy | $^n$Hex | 16b |
| 51 | $^n$Hex | Cy | 16b |
| 63 | $(CH_2)_9OSiMe_3$ | $^n$Pr | 16b |
| 60 | $(CH_2)_6OAc$ | Et | 16c |

stereo- and regiodefined conjugated dienes. Indeed, both Ni- or Pd-catalyzed cross-coupling of alkenylalanes with alkenyl iodides proceeded as desired.[19b] 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 ≥97%, mostly >99%, where the corresponding Ni-catalyzed reactions showed the formation of undesirable stereoisomers up to 10%.[19b] Our literature survey revealed that there was one paper by Murahashi[8a] reporting four cases of the Pd-catalyzed Grignard cross-coupling in 1975. We later learned that two other contemporaneous papers by Ishikawa[8c] and Fauvarque[8d] 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,[19] *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.*[19b]

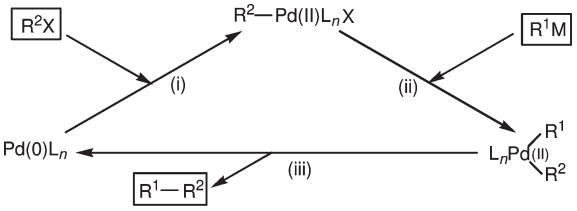
Sensing that the major player in the Pd-catalyzed cross-coupling might be Pd rather than the stoichiometric quantity of a metal countercation (M) and that the main role of M of $R^1M$ in Scheme 1 might be to effectively feed $R^1$ to Pd, 10 or so metals were screened by using readily preparable 1-heptynylmetals containing them. As summarized in Table 2,[3a,20] we not only confirmed our earlier finding that Zn was highly effective[8e] 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[5b] 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 organometals containing B and Sn began in 1979.[4c,d,5c,d]

**TABLE 2. Reactions of 1-Heptynylmetals with *o*-Tolyl Iodide in the Presence of $Cl_2Pd(PPh_3)_2$ and $^iBu_2AlH$**




| 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 |
| $BBu_3Li$ | 25 | 3 | 10 | 76 |
| **$BBu_3Li$** | **reflux** | **1** | **92** | **5** |
| $Al^iBu_2$ | 25 | 3 | 49 | 46 |
| $AlBu_3Li$ | 25 | 3 | 4 | 80 |
| $AlBu_3Li$ | reflux | 1 | 38 | 10 |
| $SiMe_3$ | reflux | 1 | trace | 94 |
| **$SnBu_3$** | **25** | **6** | **83** | **6** |
| $ZrCp_2Cl$ | 25 | 1 | 0 | 91 |
| $ZrCp_2Cl$ | reflux | 3 | 0 | 80 |

**SCHEME 3**




(i) oxidative addition, (ii) transmetalation, (iii) reductive elimination

$R^1$, $R^2$ = C groups. X = I, Br, Cl, OTf, etc. M = metal countercation.

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

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

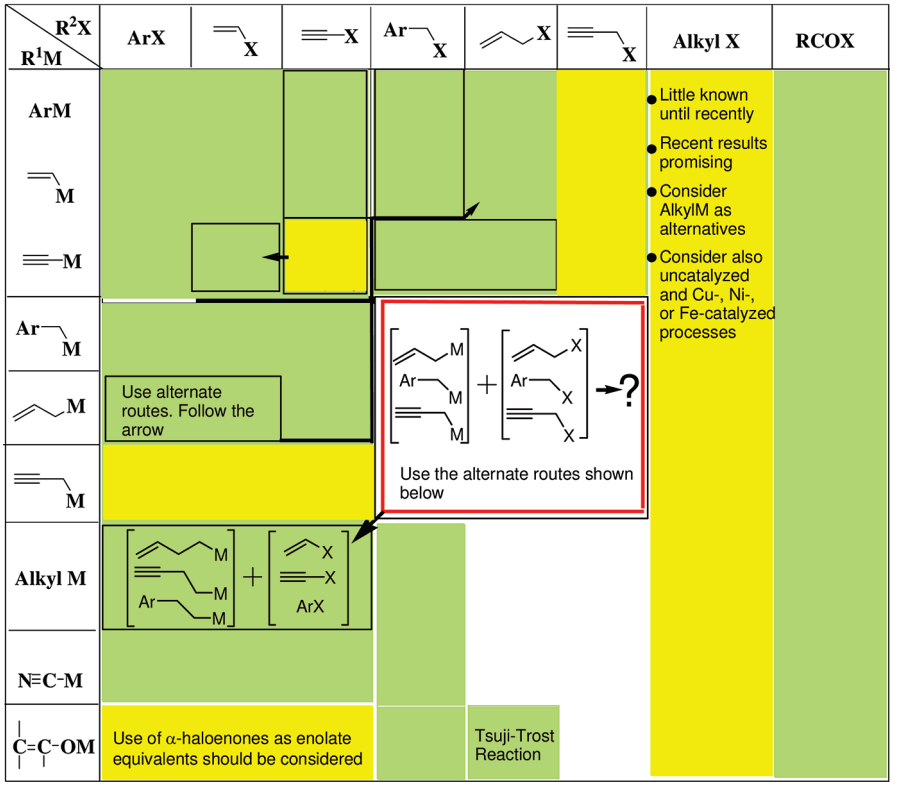
On the basis of a "three-step" mechanism consisting of (i) oxidative addition of $R^2X$ to $Pd(0)L_n$ species, where $L_n$ represents an ensemble of ligands, (ii) transmetalation between $R^2Pd(II)L_nX$ and $R^1M$, and (iii) reductive elimination of $R^1R^2Pd(II)L_n$ to give $R^1R^2$ (Scheme 3) widely accepted as a reasonable working hypothesis,[3–5,8,11] 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.

A couple of dozen papers published by us during the first several years in the 1980s on Pd-catalyzed (i) alkylation with alkylmetals,[21] (ii) cross-coupling between aryl, alkenyl, or alkynyl groups and benzyl, allyl, or propargyl groups,[22] (iii) the use of heterosubstituted aryl, alkenyl, and other $R^1M$ and $R^2M$,[21d,23] as well as acyl halides,[24] and (iv) allylation of metal enolates containing B and Zn that are not extra-activated by

**TABLE 3. LEGO Game Approach to C−C Bond Formation via Pd-Catalyzed Cross-Coupling Reactions**

$R^1M + R^2X \xrightarrow{\text{cat. } PdL_n} R^1{-}R^2 + M{-}X$ (Thermodynamic sink!)

$R^1$, $R^2$ = C group. See below. **M** = Mg, Zn, B, Al, In, Si, Sn, Cu, Mn, Zr, etc. **X** = I, Br, Cl, F, OTs, OTf, etc.
**M & X = Regio- & stereo-specifiers, which permit a genuine LEGO Game avoiding addition-elimination.**




the second carbonyl group[25] 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 progresses made in this area have 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, one modern and the other conventional, methods are mostly complementary rather than competitive with each other. As is clear from Table 3, approximately half of the seventy-two classes of cross-coupling listed in Table 3 generally proceed not only in high yields but also in high selectivity (≥98%) in most of the critical respects. As further detailed later, in approximately two dozen other classes of cross-coupling, the reactions generally proceed 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 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,[8b,26] 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.[8,11] 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 for allowing Pd to efficiently participate in the putative three-step catalytic cross-coupling cycle (Scheme 3). Indeed, under the stoichiometric conditions, alkali metals and Mg are often as effective as or even more effective than Zn and other metals.[27] 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 preassembly 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[8,11] 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[28] 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.[4]

**(2) Pd as the Optimal Catalyst Component.** Although Cu,[29] Ni,[11,13,19,30] Fe,[31] 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 ability to readily interact with nonpolar $\pi$-bonds, such as alkenes, alkynes, and arenes, leading to facile, selective, and often reversible oxidative addition, transmetalation, and reductive elimination shown in Scheme 3 and discussed later in some detail.

In contrast with the high reactivity of proximally $\pi$-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 nonconventional 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.[32]

But, why is Pd so well suited for the 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.[33] 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[12,34] 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.[34] Thus, for example, the reactions of phenylzinc bromide with *p*-iodotoluene and of (*E*)-1-decenylzinc 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 ≥97% and 80% yields, respectively.[34] At these levels, not only the 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 $R^1M$ were, in fact, preceded by the $R^1H$ versions, namely Heck alkenylation[35] and Heck−Sonogashira alkynylation.[36] Thus, evolution of the cross-coupling version took place in the $R^1H$-to-$R^1M$, rather than $R^1M$-to-$R^1H$, direction. Despite some inherent advantages associated with the $R^1H$ versions over the corresponding $R^1M$ versions, the synthetic scopes of the $R^1H$ versions are generally more limited than the $R^1M$ versions, as briefly summarized below.[37] Such differences must be clearly delineated for potential users of these reactions. At the same time, efforts to continuously expand the scopes of satisfactory protocols for all available synthetic options must be made. Clearly, most, if not all, of the good and viable synthetic methods are complementary with each other, and synergistic development and applications would be highly desirable. To this end, however, it is critically needed to delineate the scope and limitations of all available satisfactory reactions for given synthetic tasks. From the perspective of synthesizing conjugated di- and oligoenes in the y(es)[2] manner, the following difficulties and limitations of Heck alkenylation must be noted: (i) the need for certain activated and relatively unhindered alkenes, such as styrenes and carbonyl-conjugated alkenes, for satisfactory results,[38] (ii) the inability to produce either pure (≥98%) *E* or *Z* isomer from a given alkene used as $R^1H$ which can be readily and fully overcome by the use of stereodefined isomerically pure (≥98%) alkenylmetals such as $R^1M$,[39] (iii) the frequent formation of undesirable regioisomeric and stereoisomeric mixtures of alkenes[35,39] 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 heterofunctional group[35c] as compared with those often exceeding $10^6$ for the corresponding $R^1M$ version, especially with Zn as M,[34] significantly affecting cost and safety factors.

Both fundamental and practical merits of using metals (M) as (a) regio- and stereospecifiers, (b) kinetic activators, and

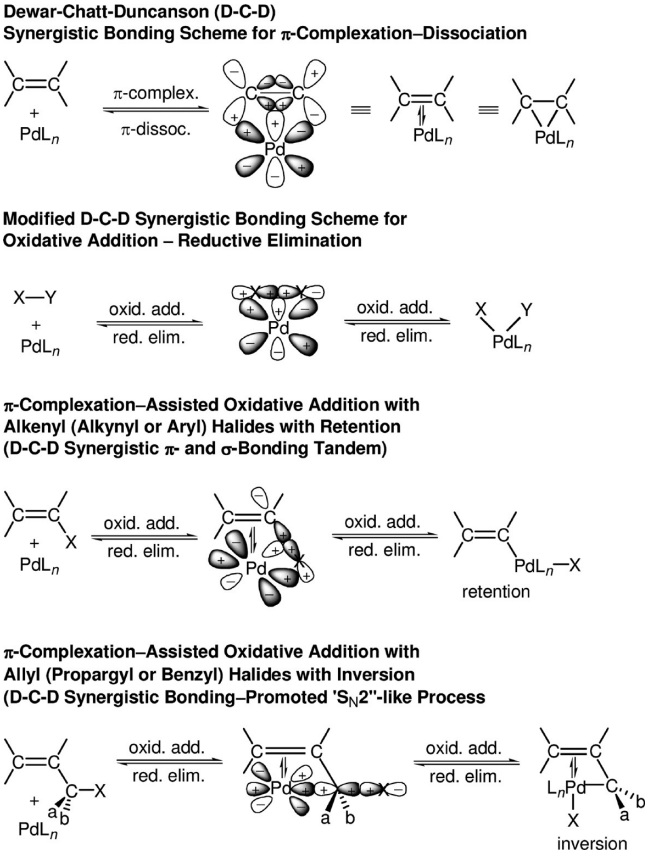
(c) thermodynamic promoters are abundantly clear, and these differences must not be overlooked. Of course, in those specific cases where the R−H versions of alkenylation and alkynylation are more satisfactory than the $R^1M$ version in the overall sense including all y(es)$^2$ factors, their use over the $R^1M$ versions may be well justified. Thus, it would still remain important and practically useful to continuously seek and develop additional $R^1H$ processes that would proceed in the y(es)$^2$ manner and would be considered superior to the $R^1M$ 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 $R^1$ and $R^2$ groups of $R^1M$ and $R^2X$, an isomerically pure single product ($R^1-R^2$) would be expected to be formed except in those cases where formation of atropisomers are possible. While the majority of $R^1$ and $R^2$ groups do retain their structural details during Pd-catalyzed cross-coupling, allylic groups, especially allylic $R^1$ in $R^1M$, and propargyl groups $R^1$ and/or $R^2$ may lose their regio- and/or stereochemical identities through allyl and propargyl−allenyl rearrangement, respectively, as discussed later in further detail. Secondary and tertiary alkyl groups are also prone to both stereoisomerization and $\beta$-elimination. However, some Pd- or Ni-catalyzed asymmetric alkylation have recently been reported to proceed stereoselectively.[40] Furthermore, the preparation of $R^1M$ and $R^2X$ 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 $R^1M$ and $R^2X$ 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[28] and Snieckus.[41]

As such, the two-stage processes for the synthesis of $R^1-R^2$ 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.[32] For example, synthesis of (*Z*)-alkenes by intermolecular cross-metathesis has just made its critical first step[42] toward becoming a generally satisfactory route to (*Z*)-alkenes in the y(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,

**SCHEME 4**

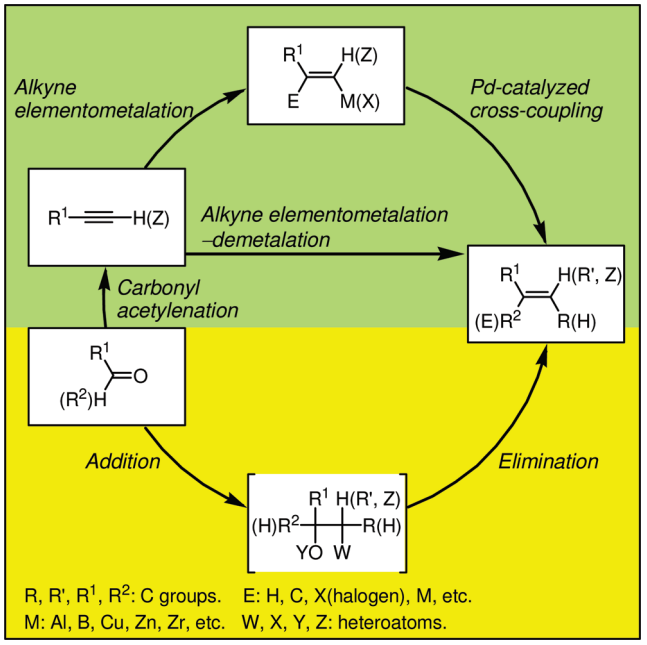



which evolved from those seminal studies with Ni,[11,43] may be applicable to other transition-metal-catalyzed processes. At the same time, it is important to be reminded that few mechanistic schemes have ever been firmly established and that they are, in most cases, not much more than useful working hypotheses for rational interpretations and predictions on the bases 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,[44] synergistic bonding of Dewar,[45] exemplified by the so-called Dewar−Chatt−Duncanson (DCD) model (Scheme 4), and the orbital symmetry theory of Woodward and Hoffmann[46] can never be overemphasized.

In the area of C−C cross-coupling in the y(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) the ability to provide simultaneously one or more each of valence-shell empty orbitals serving as LUMOs and filled nonbonding orbitals serving as HOMOs (Scheme 4) and (ii) the 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 nonbonding orbitals, carbenes are known to readily interact with nonpolar $\pi$-bonds and even

**SCHEME 5**




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 nonbonding orbital together with an empty orbital.

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., $ClRh(PPh_3)_3$ and $Cl_2Pd(PPh_3)_2$, *but also reversibly formed in redox processes permitting high catalyst TONs* often exceeding a million or even a billion.[12,34] We 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 $Pd(^tBu_3P)_2$. In the oxidative addition step in Scheme 3, *Pd must not only act like singlet carbene to generate $\pi$-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 $\sigma$-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.

**TABLE 4. Classification and Definition of 10 Types of Alkenyl Groups**

| Type | Alkenyl Descriptor | Structure | Regiodefined? | Stereodefined? |
|---|---|---|---|---|
| I | Vinyl | $H_2C{=}CH-$ | No | No |
| II | α-Monosubstituted | $H_2C{=}C(R)-$ | Yes | No |
| III | (*E*)-β-Monosubstituted |  | Yes | Yes |
| IV | (*Z*)-β-Monosubstituted |  | Yes | Yes |
| V | α, β-*cis*-Disubstituted |  | Yes | Yes |
| VI | α, β-*trans*-Disubstituted |  | Yes | Yes |
| VII | (*E*)-β, β'-Disubstituted[a] |  | Yes | Yes |
| VIII | (*Z*)-β, β'-Disubstituted[a] |  | Yes | Yes |
| IX | (*E*)-α, β, β'-Trisubstituted[a] |  | Yes | Yes |
| X | (*Z*)-α, β, β'-Trisubstituted[a] |  | Yes | Yes |

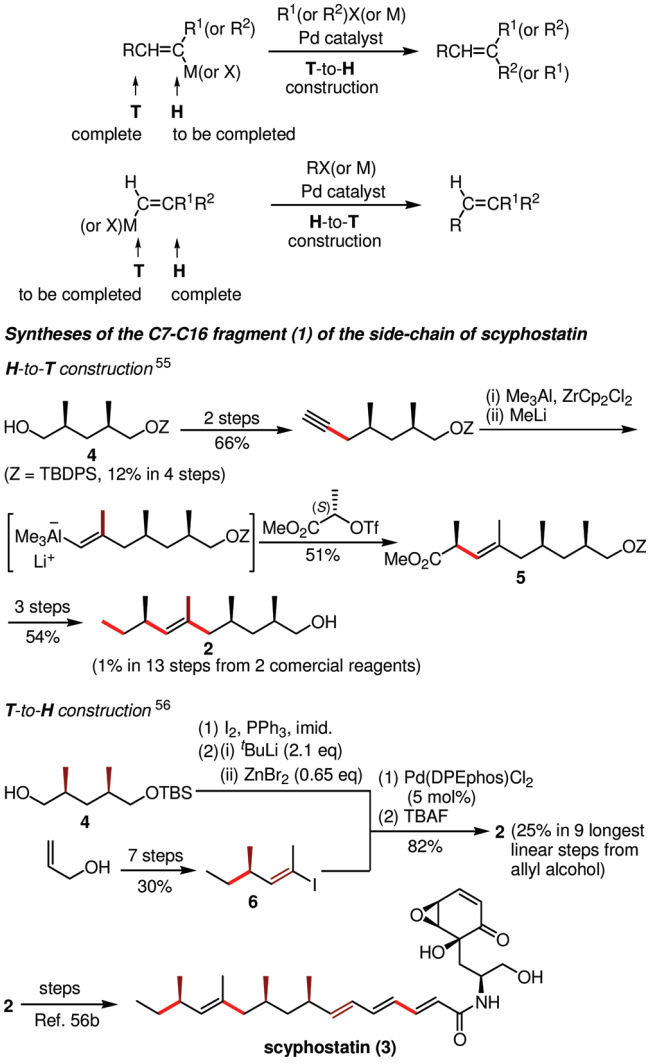
[a] $R^L$ takes a higher priority than $R^S$ according to the Cahn−Ingold−Prelog rule.

## Alkyne Elementometalation−Pd-Catalyzed Cross-Coupling Routes to Alkenes

**Historical Background of Alkene Syntheses.** Before the advent of the Pd-catalyzed alkenylation[19,47] and alkynylation[37] 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 Wittig reaction[48] and its variants, such as Horner−Wadsworth−Emmons reaction[49] and its later modifications including *Z*-selective Still−Gennari[50] and Ando[51] versions as well as (b) Peterson olefination[52] and its variants including Corey−Schlessinger−Mills methacrylaldehyde synthesis[53] and (c) Julia[54] 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 y(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 (≥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 (≥98%) stereoselectivity and often tends to be regiochemically capricious as well.

As discussed earlier, the Pd-catalyzed alkenylation is thought to proceed generally via reductive elimination, although some involving the use of relatively nonpolar C−M bonds, such as C−B, C−Si, and C−Sn, are known to proceed at least partially

**SCHEME 6**

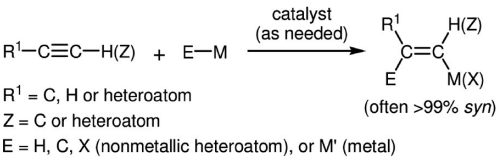



via carbometalation−$\beta$-elimination. In sharp contrast with $\beta$-elimination, reductive elimination, which is predominantly a $\sigma$-bond process, can proceed in most cases with full retention of all alkenyl structural details (see later discussions for significant exceptions due to the intermediacy of allylmetals). 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 y(es)[2] criteria. Thus, the Pd-catalyzed alkenylation has evolved since the mid-1970s into arguably the most general and highly selective (≥98%) method of alkene synthesis known to date (Scheme 5).

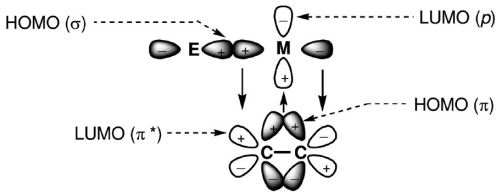
At this point, it is both useful and important to classify the alkenyl groups, $R^1$ and/or $R^2$ in $R^1M$ and/or $R^2X$, into the following 10 structural types (Table 4). Since our attention is mainly focused on those cases where both regio- and stereochemical details critically matter, no intentional discussion of type I and II alkenyl groups is presented. Although type IX and X trisubstituted alkenyl groups for the syntheses of tetrasubstituted alkenes are of interest to us, those that are

**SCHEME 7**

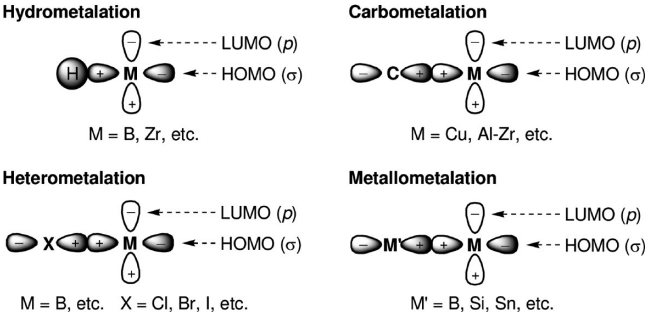
*Plausible concerted mechanism for syn-elementometalation*




*Synergistic HOMO-LUMO interaction schemes for elementometalation*




*Structures of various addends*




acyclic are substantially more scarce than di- and trisubstituted alkenes in nature. Perhaps, in part, for this reason, the methodology for their syntheses is still underdeveloped and therefore will be only briefly discussed.

In this paper, a relatively brief discussion of well-developed methods for the preparation of type III and IV $\beta$-monosubstituted alkenyl derivatives and their use for the syntheses of $\alpha,\beta$-disubstituted alkenes will be followed by more detailed discussion of the preparation of type V−VIII trisubstituted alkenyl derivatives (highlighted in yellow in Table 4) and their use for the syntheses of trisubstituted alkenes. In the syntheses of trisubstituted alkenes via type V or VI alkenyl derivatives, construction of the monosubstituted end, conveniently termed here the tail and abbreviated as **T**, is completed first, and the disubstituted end, termed the head and abbreviated as **H**, is completed in the final Pd-catalyzed cross-coupling step, i.e., **T**-to-**H** construction. Those via type VII or VIII alkenyl groups then involve **H**-to-**T** construction (Scheme 6). As examples of those cases where the modes (or directions) of construction are important, the following pair of syntheses of the C7−C16 fragment (**2**) of the side-chain of scyphostatin (**3**) may be presented (Scheme 6). In the earlier **H**-to-**T** construction,[55] **4** (Z = TBDPS) was sequentially tosylated, ethynylated, methylaluminated, and subjected to an "$S_N2$" reaction with (*S*)-$EtO_2CCH(Me)OTf$ to give **5** in 34% yield in three steps, which was then converted to **2** in 54% yield in three steps or in 18% yield in six linear steps from **4**. In the **T**-to-**H** construction,[56] **4** (Z = TBS) was iodinated and cross-coupled with **6** to give **2** just in two steps in 82% yield after deprotection, while the key intermediate **6** was prepared from allyl alcohol in 30% yield over seven steps.

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

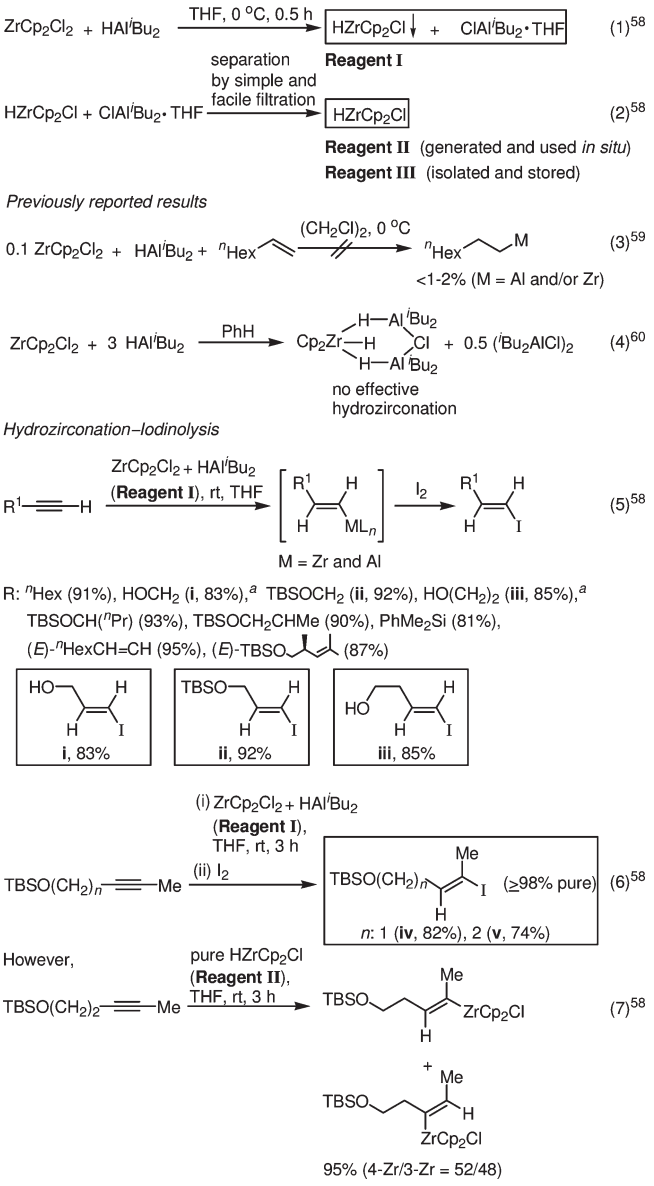
| *syn*-Elementometalation | B | Zr | Al | Cu |
|---|---|---|---|---|
| *syn*-Hydrometalation (Types III-VI) | • Widest scope and applicablity.<br>• Most tolerant of carbonyl and other heterofunctional groups.<br>• Relatively slow in Pd-cat. cross-coupling.<br>• Prone to π-addition–elimination leading to regio- and stereo-scrambling.<br>• Recent cross-coupling procedures increasingly satisfactory. | • Reasonable scope.<br>• Highly regioselective with $R^1$—≡—H, esp. with conjugated terminal enynes and some internal alkynes, etc.<br>• Recent preparative procedure of $HZrCp_2Cl$ very convenient.<br>• Highest reactivity in Pd-cat. cross-coupling among the four metals listed. | • More limited than B or Zr.<br>• Alkynyl H or halogen abstraction problematic. | • Relatively little developed. |
| *syn*-Carbometalation (Types VII&VIII) | • Uncatalyzed four-centered carboboration essentially unknown. | • Zr alone tends to undergo cyclic carbozirconation, but it is a good metal as catalyst for carboalumination. | • Zr-cat. methylalumination (ZMA) is of broad scope with respect to $R^1$ of $R^1$—≡—H and of very high synthetic value.<br>• Some benzyl, allyl, and higher *n*-alkylaluminums also react readily, but selectivity problematical.<br>• >150 complex natural prodcuts prepared.<br>• Al used together with Zn in some cases is very satisfactory in Pd-cat. cross-coupling. | • Primary alkyl-cupration useful.<br>• Types VII and VIII as well as IV alkenyl derivatives accessible.<br>• Methylcupration sluggish. Use ZMA instead.<br>• Cu-Zn combination very good in Pd-cat. cross-coupling. |
| *syn*-Halometalation (Types VII&VIII) | • Bromoboration of alkynes facile and broadly applicable.<br>• A wide reange of Type VII and VIII alkenyl derivatives are accessible.<br>• With ethyne Type III alkenyl derivatives are accessible, but its use needs justification.<br>• Recent procedures for both bromoboration and subsequent Pd-cat. cross-coupling very promising (see Scheme 9). | • Appears to be unknown. | • Appears to be unknown. | • Appears to be unknown. |

**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 π*- and π-orbital pair of alkynes and alkenes, as shown in Scheme 7 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 EMs 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 nontoxic 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 exploration. Likewise, transition-metal-catalyzed elementometalation reactions of Si, Ge, and Sn are promising,[57] but their adoption will have to be fully justified through objective overall comparisons with B, Al, Zr, and Cu. In this paper, no specific discussion of alkyne metallometalation is intended.

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 development of an operationally simple, economical, clean, and satisfactory reaction of $ZrCp_2Cl_2$ with 1 equiv of $^iBu_2AlH$ in THF for generating genuine $HZrCp_2Cl$ (Scheme 8).[58]

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[61] 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.[62] This difficulty was overcome for the single-most important case of alkyne methylalumination through the

## SCHEME 8

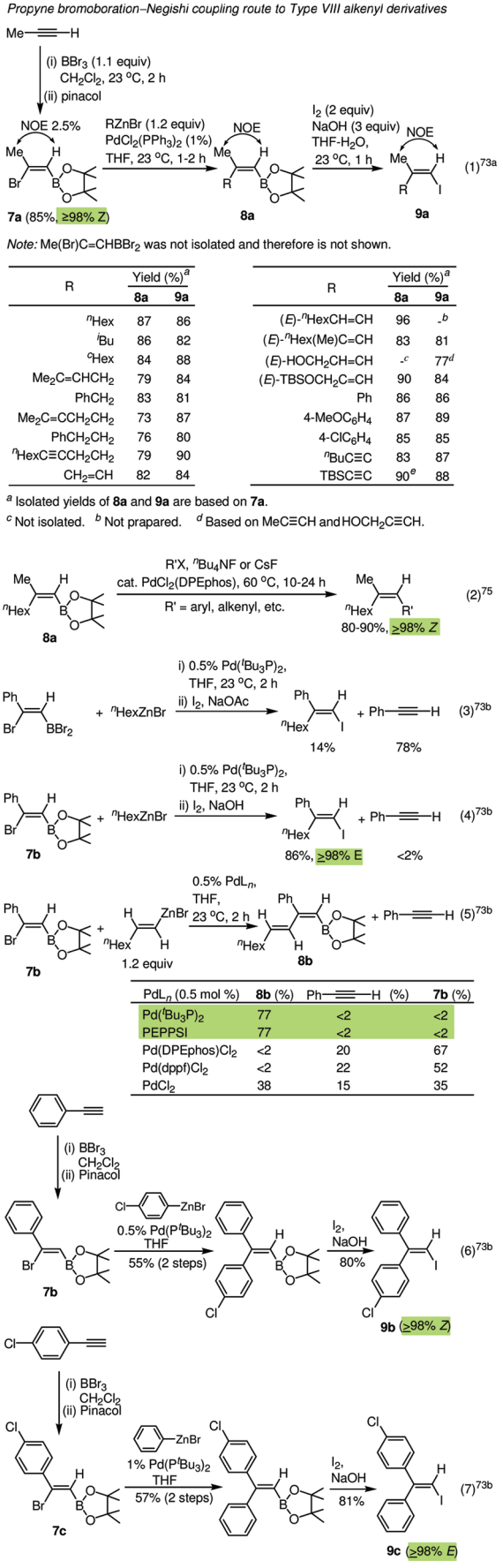



[a] An additional 1 equiv of $HAl^iBu_2$ was used to metalate the OH group.

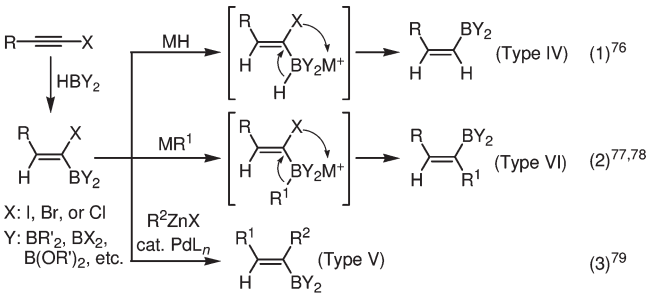
discovery and development of the Zr-catalyzed methylalumination of alkynes with $Me_3Al$ (ZMA reaction).[13a,63,64] Ethyl- and higher alkylaluminums[64,65] as well as those containing allyl and benzyl groups[66] react readily but display disappointingly low regioselectivity ranges due mainly to intervention of cyclic carbozirconation,[65] which must be further improved.

In view of the above-mentioned limitations associated with carbometalation reactions, alkyne haloboration reactions discovered by Lappert[67] in the early 1960s and developed by Suzuki[68] in the 1980s are of considerable interest. In particular, the alkyne bromoboration−Negishi couping tandem process[69] promised to provide a broadly applicable method for the head-to-tail (**H**-to-**T**) construction of various types of trisubstituted alkenes (Scheme 9). In reality, however, there were a number of undesirable limitations, of which the following were some of the most critical: (i) formation of (*E*)-*β*-haloethenylboranes through essentially full stereoisomerization,[70] (ii) partial

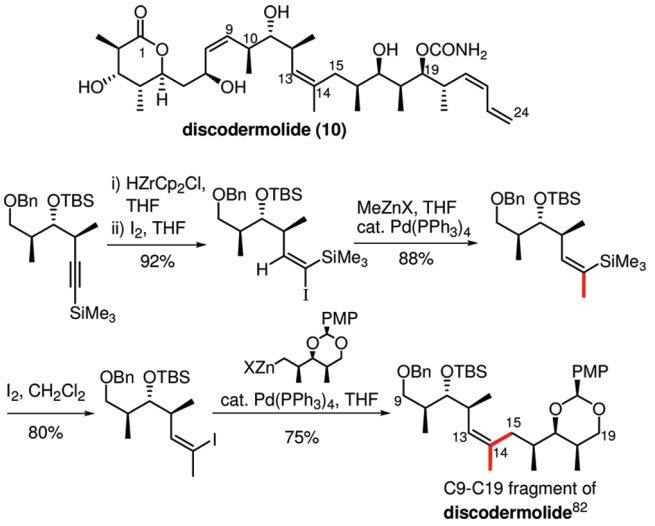
## SCHEME 9



**SCHEME 10**




**SCHEME 11**

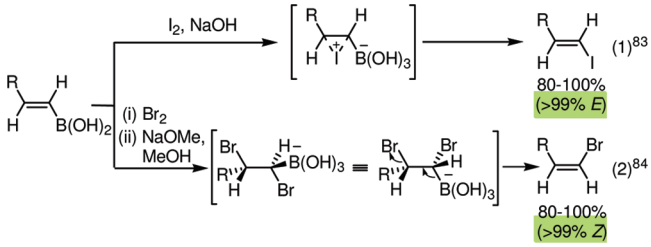



stereoisomerization (≥10%) in the arguably single-most important case of propyne haloboration,[71] competitive and extensive $\beta$-dehaloboration to give the starting alkynes in cases where 1-alkynes contain unsaturated aryl, alkenyl, and alkynyl groups, and sluggish second Pd-catalyzed cross-coupling reactions under the reported Suzuki coupling conditions.[69] To avoid this difficulty, use of the second Negishi coupling via B→I[72−74] and even B→I→Li[74] transformations have been reported as more satisfactory, if circuitous, alternatives.

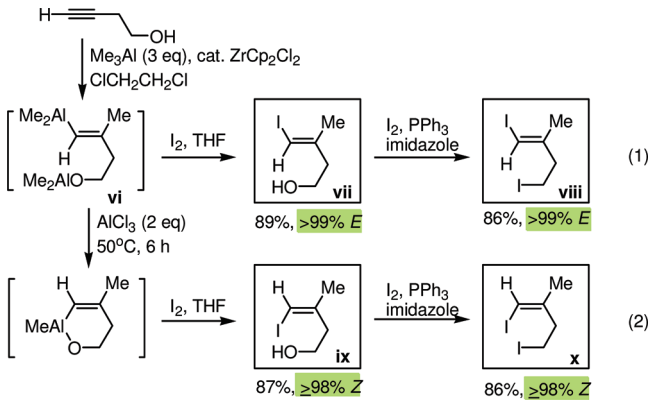
Although no investigation of the item (i) has been attempted, highly satisfactory procedures have been developed for fully avoiding the difficulty described in the item (ii)[73a] (eq 1, Scheme 9) and substantially improving the second-stage Pd-catalyzed cross-coupling by the direct use of alkenylborane intermediates[75] (eq 2, Scheme 9). Additionally, a major step toward 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[74b] (eqs 4−7, Scheme 9). At present, however, use of conjugated enynes and diynes in place of arylethynes appears to be even more challenging than the cases of arylethynes, 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.

**SCHEME 12**




**SCHEME 13**



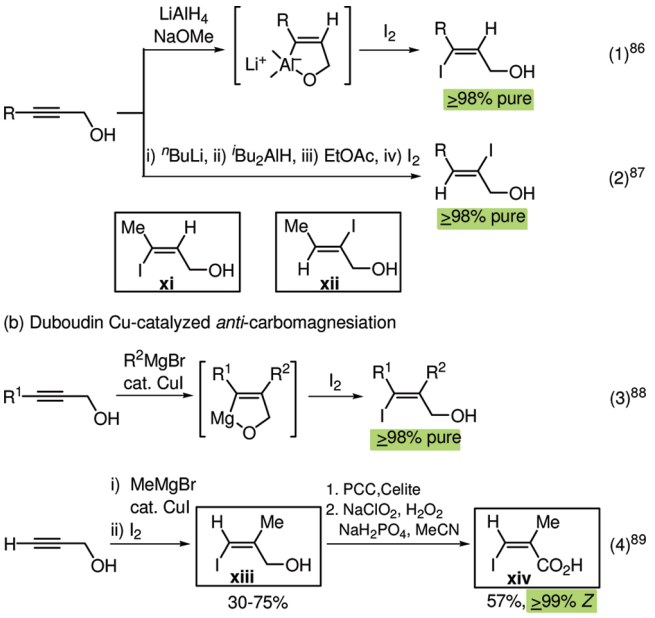

**Alkyne *syn*-Elementometalation Followed by Stereo- and/or Regioisomerization.** (**a**) ***syn*-Hydroboration of 1-Halo-1-alkynes.** *syn*-Hydroboration of internal alkynes tends to give a mixture of two possible regioisomers. In cases where 1-halo-1-alkynes are used as internal alkynes, the reaction is nearly 100% regioselective placing B at the halogen-bound carbon. The resultant (*Z*)-α-haloalkenylboranes can be used to prepare (i) (*Z*)-1-alkenylboranes (type IV),[76] (ii) (*Z*)-α,β-disubstituted alkenylboranes (type V),[79] and (iii) (*E*)-α,β-disubstituted alkenylboranes (type VI)[77,78] as summarized in Scheme 10.

(**b**) ***syn*-Hydrometalation of 1-Metallo-1-alkynes.** *syn*-Hydrozirconation of 1-silyl-1-alkynes[80] and 1-boryl-1-alkynes[81] gives 1,1-dimetallo-1-alkenes. By taking advantage of the higher reactivity of the C−Zr bond in various reactions, such as protonolysis, iodinolysis, and Pd-catalyzed cross-coupling, types IV and VI alkenylmetals and other derivatives can be obtained, as demonstrated in Scheme 11.[82] Many other possibilities await further explorations.

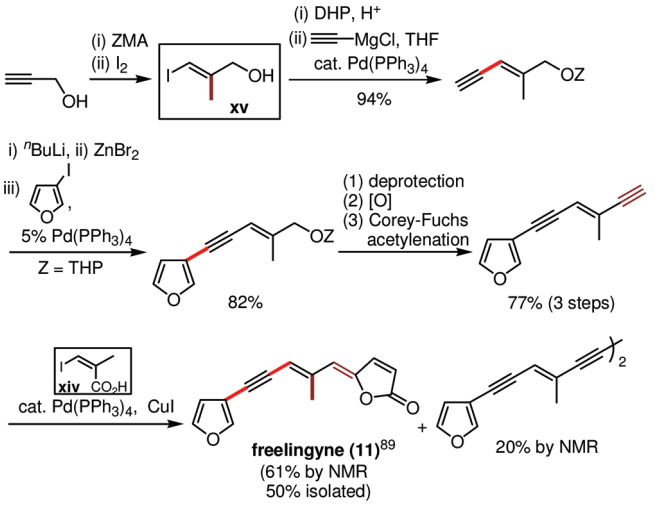
(**c**) ***syn*-Hydroboration of 1-Alkynes Followed by Halogenolysis with Either Retention or Inversion.** Hydroboration of 1-alkynes followed by iodinolysis proceeds with retention to give (*E*)-1-iodoalkenes (type III) of >99% purity,[83] whereas the corresponding brominolysis in the presence of NaOMe in MeOH produces the stereoinverted *Z*-isomer (type IV) of >99% purity[84] (Scheme 12).

(**d**) ***syn*-Zr-Catalyzed Carboalumination (ZMA) of Proximally Heterofunctional Alkynes Followed by Stereoisomerization.** The ZMA reaction of homopropargyl alcohol followed by treatment with $AlCl_3$ at 50 °C for several hours provides the corresponding *Z* isomer.[85] 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 13).

**SCHEME 14**




**SCHEME 15**

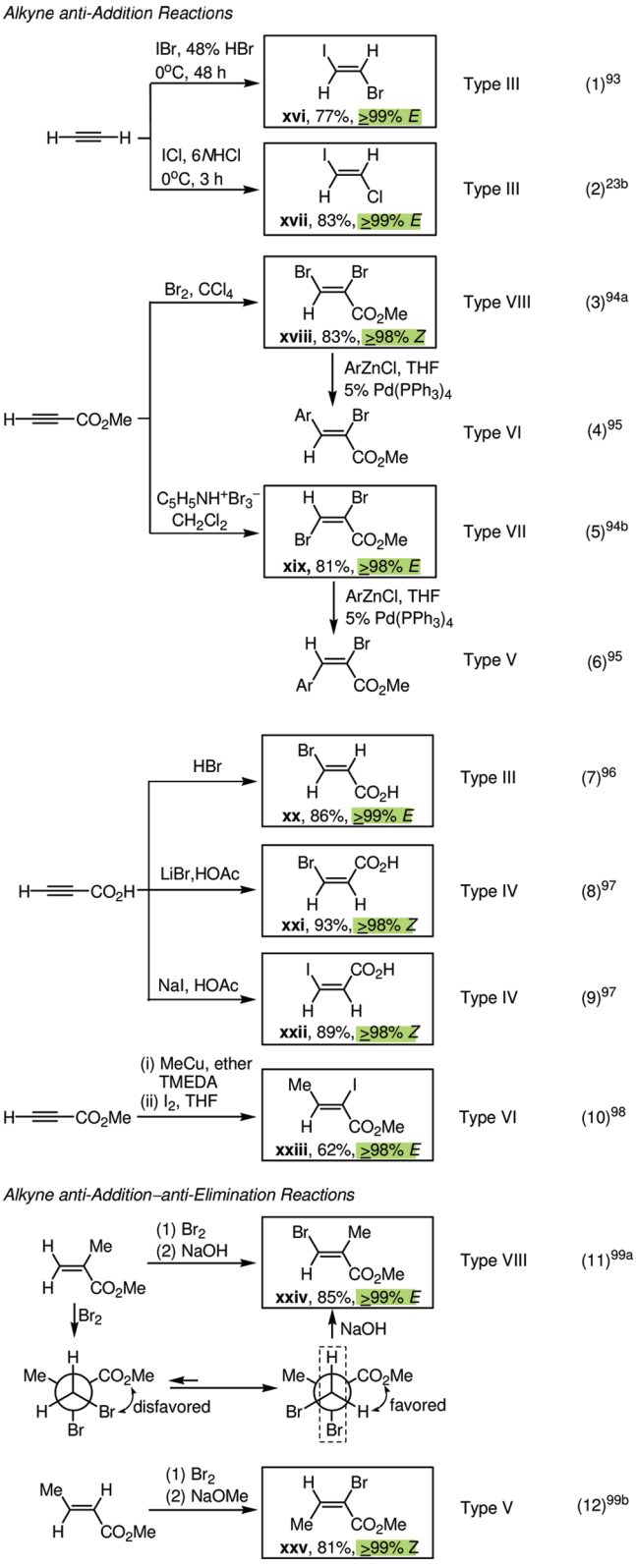



**Highly Selective *anti*-Addition Reactions of Alkynes.** The *syn*-elementometalation reactions of alkynes discussed above may be supplemented with various other addition reactions of alkynes, of which the following two classes of reactions have been particularly useful: (i) *anti*-hydrometalation and *anti*-carbometalation reactions of proximally heterosubstituted alkynes and (ii) conventional *anti*-addition reactions of alkynes with readily polarizable compounds (X−Y).

**(i) *anti*-Hydrometalation and *anti*-Carbometalation Reactions of Proximally Heterosubstituted Alkynes.** A fair number of proximally heterosubstituted internal alkynes react with *coordinatively saturated* metal-containing reagents (E−M) to undergo highly *anti*-selective (often ≥98% *anti*) elementometalation reactions. Some representative examples of high synthetic values are shown in Scheme 14.

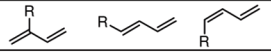
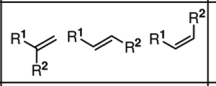
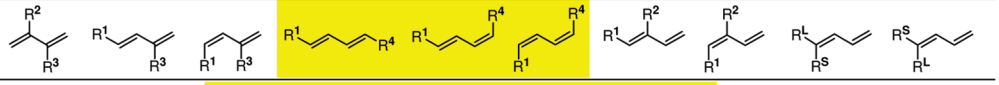
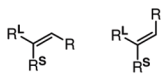
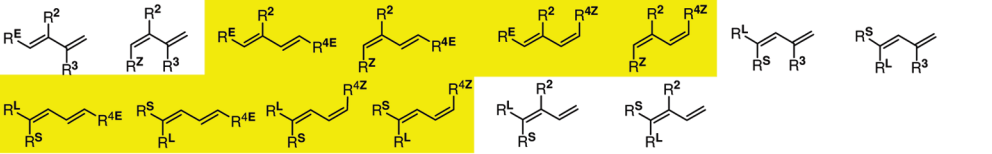
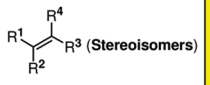
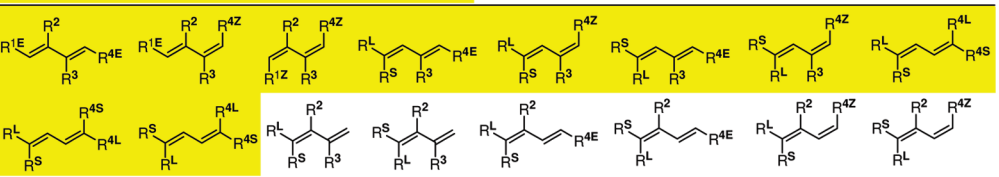
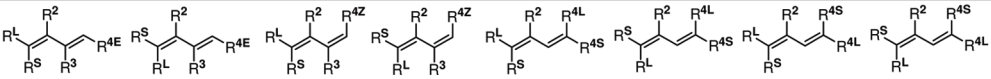
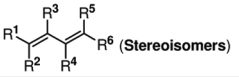
Although the Duboudin *anti*-carbomagnesiation of propargyl alcohol itself needs to be further improved, this reaction (eq 4 in Scheme 14) and the ZMA reaction of propargyl alcohol, which also needs further improvement,

**SCHEME 16**




can serve as useful synthons, as exemplified by their application in a highly stereoselective synthesis of freelingyne[89] (Scheme 15). The Sonogashira[90] alkynylation-based Lu−Huang−Ma[91] alkynylation−lactonization cascade process was plagued by side reactions, especially alkyne homodimerization.

**TABLE 6. Various Conceivable Structural Types of Dienes**[a−c]

| | **Monoenes** (8+ Types) | **1,3-Dienes** (53+ Types. The number of conceivable structural types exponentially increases as the the number of oligo- and polyenes) |
|---|---|---|
| **Unsubstituted** |  |  |
| **Monosubstituted** |  |  |
| **Disubstituted** |  |  |
| **Trisubstituted** |  |  |
| **Tetrasubstituted** |  (Stereoisomers) |  |
| **Pentasubstituted** | None |  |
| **Hexasubstituted** | None |  (Stereoisomers) |

[a]Although only the conjugated acyclic diene structures are shown, they may be readily modified to generate the corresponding 1,4- and 1,5-dienes. In this paper, no systematic discussion of cyclic structures is intended. [b]Attention in this paper is focused on those 21 dienes (and oligoenic homologues) containing both regio- and stereodefined type III−VIII alkenyl groups highlighted in yellow. [c]$R^L$ represents a group of higher priority relative to $R^S$ according to the Cahn−Ingold−Prelog rule.

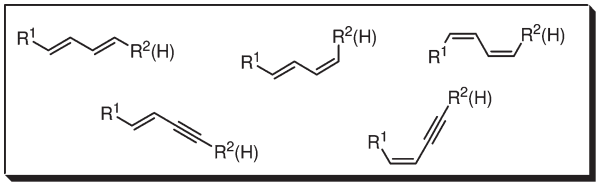
Although not applied to the synthesis of freelingyne, the difficulties associated with this protocol have been resolved by recent development of Negishi alkynylation−Ag-catalyzed lactonization two-step tandem process.[37,92]

**(ii) Conventional *anti*-Additions of Alkynes of High Regio- and/or Stereoselectivity.** Various polar and readily polarizable halogen-containing reagents (X−Y) are known to add readily to alkynes and alkenes. As long as they are highly (≥98%) regio- and/or stereoselective, they may serve as useful cross-coupling partners, $R^1M$ and/or $R^2X$. In the cases of alkene addition, they must also participate in satisfactory elimination reactions. Those di- and triheterofunctional alkenyl reagents **i**−**xxv** shown in boxes (Schemes 8 and 13−16) have been widely used as type III−VIII alkenyl synthons, especially in complex natural product syntheses, as demonstrated throughout this paper.

## Highly (≥98%) Selective and Efficient Syntheses of Dienes, Enynes, and Their Oligomeric Homologues with Emphasis on Those of Biological and Medicinal Interest

In the preceding sections, the basic framework of alkyne elementometalation−Pd-catalyzed cross-coupling route to alkenes in the y(es)$^2$ manner was briefly discussed. In this section, its applications to the syntheses of dienes, enynes and their oligomeric homologues will be discussed with emphasis on those of biological and medicinal interest performed by the authors' group. At this point, it should be reemphasized that the numbers of possible stereo- and regioisomers of dienes and oligoenes increase exponentially as the degree of oligomerization increases in sharp contrast with oligoynes, as indicated in Table 6 for conjugated dienes. There are more than 50 types of both stereo- and regio-defined conjugated dienes. Gratifyingly, it does appear that, as long as the two required alkenyl groups are obtainable in the y(es)$^2$ manner, Pd-catalyzed cross-coupling, especially under the Negishi and/or Suzuki coupling conditions, will, in the majority of cases, provide the desired dienes also in the y(es)$^2$ manner, as detailed below.

**(1) Conjugated Dienes, Enynes, and Their Oligomeric Homologues Containing One or More Type III and/or IV Alkenyl Groups.**



As mostly discussed previously, type III alkenyl derivatives, i.e., (*E*)-$R^1CH{=}CHM$(or X), are widely and satisfactorily generated by (a) alkyne hydrometalation (M = B, Zr or, in some cases, Al, etc.) (Table 5, Scheme 8), (b) polar addition reactions to generate **xvi**, **xvii**, and **xx** (Scheme 16), and additionally, (c) *anti*-bromoboration of ethyne[70] followed by Negishi coupling (eq 1, Scheme 17).

On the other hand, type IV alkenyl derivatives may be prepared by (a) Normant alkylcupration of ethyne[61b] (eq 2, Scheme 17), (b) Zr-catalyzed alkylalumination of ethyne (eq 3, Scheme 17), (c) *syn*-hydroboration of 1-halo-1-alkynes followed by hydride-induced inversion of configuration[76] (Scheme 10), (d) hydroboration of 1-alkynes followed by brominolysis (but not iodinolysis) with inversion,[84] and (e) *syn*-hydrozirconation or *syn*-hydroalumination of 1-boryl- or 1-silyl-1-alkynes followed by protonolysis of the C−Al or C−Zr bond[80,100,101] (eq 4, Scheme 17).

The methods listed above are by no means intended to be exhaustive, even though most, if not all, of the type III and IV alkenyl reagents may now be prepared by one or more of them. Some other known routes to them that are by and large either not yet well-developed or not selectively applicable to the syntheses of acyclic unsymmetrically substituted alkenes are not cited here. It should also be mentioned that further explorations and developments in this general area are very desirable.

**Critical Comparison of Negishi and Suzuki Versions of the Pd-Catalyzed Alkenylation, Heck Alkenylation, and Horner−Wadsworth−Emmons (HWE) Olefination as Well as Its Still−Gennari and Ando Modifications.** For rigorous comparison of some of the widely used methods for the syntheses of conjugated dienes and oligoenes, syntheses of the four possible isomers of ethyl undeca-2,4-dienoates (**13-16**) by (i) Negishi alkenylation (Zr and/or Zn),[3] (ii) Suzuki alkenylation,[4] (iii) Heck alkenylation,[35] (iv) HWE olefination,[49] and (v) its Still-Gennari[50] or Ando modification[51] have been carried out. The choice of the conjugated dienoic esters was dictated by the definition of the carbonyl olefinations, i.e., iv and v, requiring α, β-unsaturated carboxylic acid derivatives. At the outset, it was noted that a report on catalyst optimization for the synthesis of ethyl (2*Z*,4*E*)-nona-2,4-dienoates by Suzuki alkenylation[4e] indicated stereoscrambling occurring to variable extents, 5−80%, at the α,β-C=C bond (Scheme 18). In contrast, all four possible stereoisomers of ethyl undeca-2,4-dienoates (**13**−**16**) were prepared in > 98% stereoselectivity by Negishi alkenylation (Scheme 19).[39a] Moreover, the catalyst turnover number (TON) for the synthesis of the 2*Z*,4*E* isomer **15** was shown to be at least $10^5$ by using 0.001 mol % of PEPPSI[39a] (pyridine-enhanced precatalyst preparation stabilization and initiation).[102] These favorable results shown in Scheme 19 prompted us to reinvestigate the stereoselectivity in the Suzuki alkenylation route to 2,4-dienoic esters, such as **15**. Although this study is still ongoing, the use of CsF or $^n$Bu$_4$NF (TBAF) as a promoter base promises to provide a widely applicable and highly selective (≥98%) Pd-catalyzed alkenylation route to various types of mono-, di-, and oligoenes.[39a] Thus, for example, **15** was obtained in 88% yield in ≥98% stereoselectivity. We then noticed in our recent literature survey that, although 2,4-dienoic esters were not prepared, Molander's alkenylation[103] with potassium alkenyltrifluoroborates prepared by treatment of alkenylboranes with $KHF_2$ of Vedejs[104] would provide selectively in 85−88% yields all four stereoisomers of 9-chloro-1-phenylnona-3,5-dienes. Further details of these seemingly related protocols are under investigation.

The practically acceptable scope of Heck alkenylation with respect to alkenyl halides is wide, but that with respect to the nonhalogenated alkene partner is rather limited, usually requiring proximally π-bonded, e.g., Ar, and/or heterofunctional, groups for satisfactory results.[38] Furthermore, in cases where stereoundefined 1-alkenes ($H_2C=CHR$) are used, only one, namely *E*, isomer can be obtained as the major product, thereby making the other isomer inaccessible via this route. In principle, stereodefined *E* or *Z* XCH=CHR may be used in place of $H_2C$=CHR. However, it has been difficult to attain a high (≥98%) stereoselectivity by using (*Z*)-BrCH=CHCO$_2$Et, as exemplified in eq 3, Scheme 20. This and related cases are currently being further clarified. Furthermore, even in favorable cases of Heck conjugated diene synthesis, the TONs reported in the literature,[35e] using 70% as the lowest acceptable product yield, have been mostly limited to $\leq 10^2-10^3$.

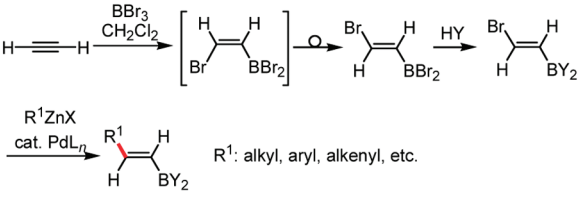
By definition, the scope of HWE as well as its Still−Gennari[50] and Ando[51] modifications are limited to the syntheses of α,β-unsaturated carbonyl derivatives. Within this limitation, HWE reactions are widely applicable and used. Unless there is at least one additional stereocontrolling factor, such as the use of aryl aldehyde, however, the reported stereoselectivity for the preparation of 2,4-dienoate esters has been typically ≤90%.[39] Using KN(SiMe$_3$)$_2$ and 18-crown-6 (≥2 equiv),[105] Still−Gennari olefination provided ≥98% isomerically pure ethyl (2*Z*,4*E*)-hex-2,4-dienoate (**17**) in 98% yield.[39] On the other hand, its capricious behaviors, especially in the syntheses of (2*Z*,4*Z*)-5-stannylpenta-2,4-dienoic esters, have also been noted. For such Sn-substituted cases, the Ando version was shown to be better than the Still−Gennari version but still only marginally satisfactory (Scheme 20).[105] This reaction has recently been applied to the synthesis of (+)-sorangicin A[106] (Scheme 20). Clearly, further methodological development in this area is highly desirable.

The current profile of various methods for the syntheses of 1,4-disubstituted conjugated dienes are summarized in Table 7. At present, the Pd-catalyzed Negishi alkenylation is the only method permitting highly (≥98%) stereoselective syntheses of all four possible 2,4-dienoic esters. Furthermore, the Pd-catalyzed alkenylation in general represented by Negishi and Suzuki coupling is the only method that can accommodate a wide variety of carbon groups without requiring carbonyl and other activating groups. Some representative earlier examples of the syntheses of natural products containing 1,4-disubstituted 1,3-dienes are shown in Scheme 21.

A brief exploration for developing Pd-catalyzed Negishi alkenylation−HWE olefination synergy has led to the development of a highly (≥98%) selective and efficient Negishi

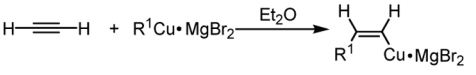
**SCHEME 17**

*anti*-bromoboration of ethyne followed by Negishi coupling[70]



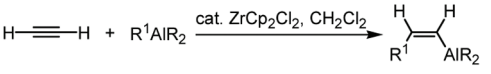

(1)

*syn*-alkylcupration of ethyne[61b]



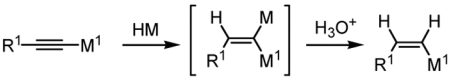

(2)

Zr-catalyzed *syn*-alkylalumination of ethyne




(3)

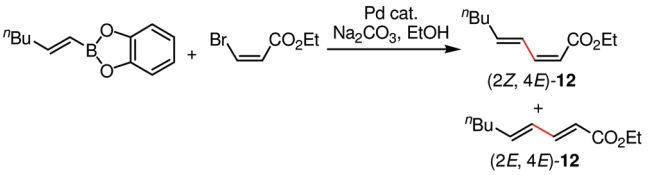
*syn*-hydrometalation of 1-metallo-1-alkynes (M = B, Si, etc.) followed by protonolysis[100, 101]




(4)

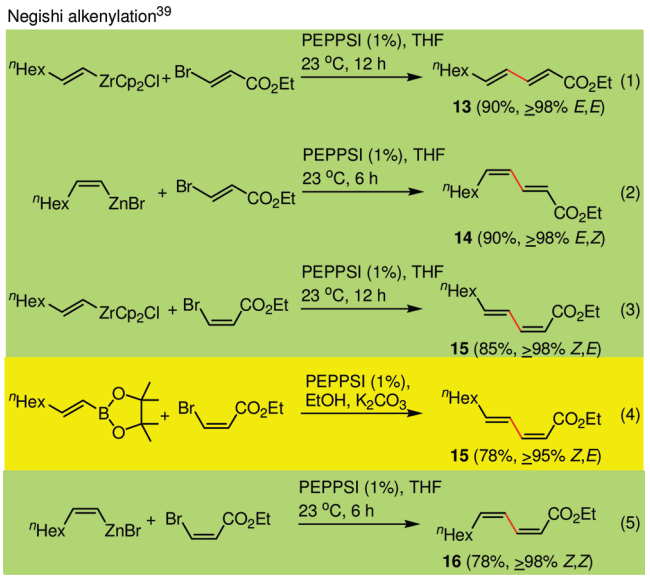
$M_1$ = $BY_2$, $SiR_3$, etc. M = Zr, Al, etc

**SCHEME 18**




| Pd catalyst | Temp (°C) | Time (h) | Total Yield (%) | 2Z, 4E (%) | 2E, 4E (%) |
|---|---|---|---|---|---|
| $Pd(OAc)_2(PPh_3)_2$ | reflux | 5 | 70 | 44 | 26 |
| $Pd(OAc)_2$(dppe) | reflux | 5 | 80 | 16 | 64 |
| $Pd(OAc)_2$(dppf) | reflux | 5 | 86 | 66 | 20 |
| $Pd(OAc)_2$(dppf) | 20 | 24 | 73 | 69 | 4 |

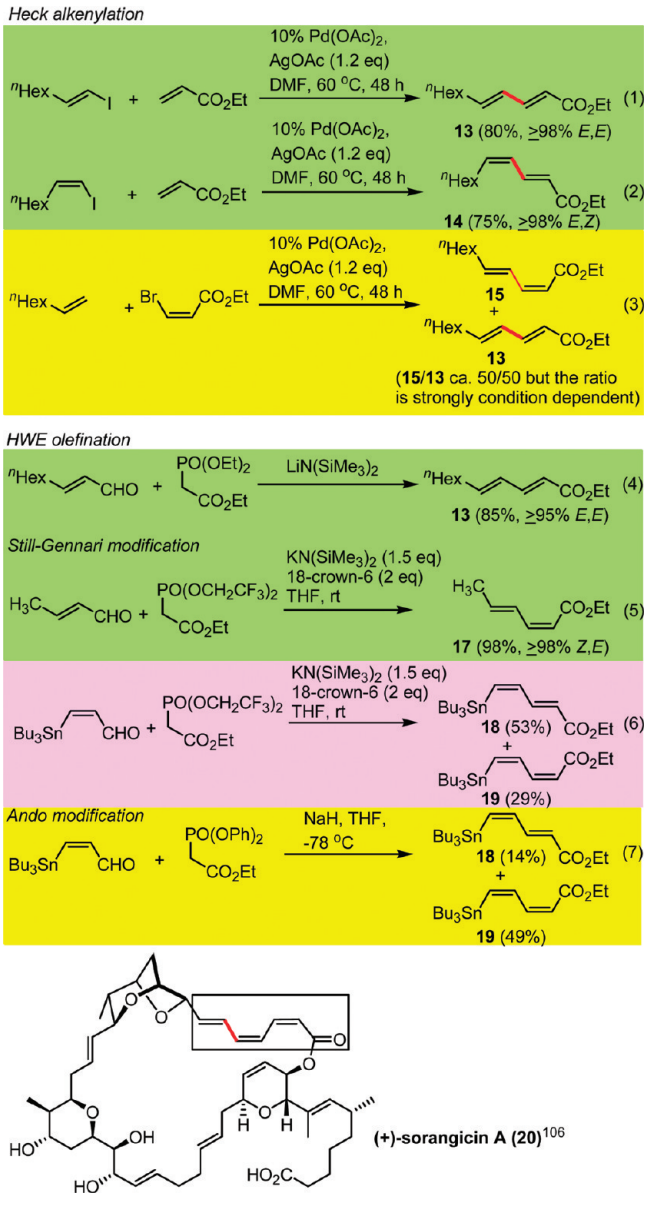
**SCHEME 19**




alkenylation route to the di- and oligoenic phosphonoesters for subsequent HWE olefination. Unfortunately, however, the stereoselectivity in the final HWE olefination step is seldom higher than 90% with alkyl-substituted aldehydes. Especially disappointing is that ≥98% pure (*Z*)-α,*β*-alkenyl groups preset by Negishi coupling (eq 4, Scheme 22) cannot be retained in the subsequent carbonyl olefination step (eqs 5 and 6, Scheme 22). On the contrary, all Pd-catalyzed Negishi alkenylation processes fully (≥98%) retains the preset stereochemistry (eq 7, Scheme 22). An exceptionally high (≥98%) stereoselectivity observed in the syntheses of (all-*E*)- and (6*E*,10*Z*)-2′-*O*-methylmyxalamides D (**27** and **28**) is a pleasant surprise to be pursued further (eqs 8 and 9, Scheme 22). Further clarification of all of the factors affecting the stereoselectivity in HWE olefination appears desirable.

**Carbonyl Olefination (Acetylenation)−Pd-Catalyzed Alkenylation Synergy.** In the preceding section, the current scope and limitations of the Pd-catalyzed alkenylation−carbonyl olefination synergy were discussed. Despite the fact that HWE olefination and its modifications often display ≤90% stereoselectivity, carbonyl olefination reactions as a whole and related carbonyl acetylenation reactions have proven to be indispensable for the synthesis of α-chiral alkenes and di- and oligoenes containing such alkenes. For the syntheses of (all-*E*)- and (6*E*,10*Z*)-2′-*O*-methylmyxalamides D shown in Scheme 22, the required ≥98% pure *γ*-chiral α,*β*-unsaturated aldehydes

**SCHEME 20**







were prepared by Corey−Schlessinger−Mills modified (CSM hereafter) Peterson olefination[52,53] and SG-modified HWE olefination,[50] respectively. The products of these reactions are also carbonyl compounds, prompting yet another round of carbonyl olefination, i.e., HWE olefination, for completion of the desired syntheses.

For carbonyl olefination−Pd-catalyzed alkenylation synergy, those reactions that permit carbonyl olefination-to-alkenylation crossover are required. Currently, Corey−Fuchs reaction[116] (eq 1, Scheme 23) is the most widely used reaction of this class. Although further improvement is desirable, iodomethylenation of Takai[117] (eq 2, Scheme 23) is promising. 1,1-Dihalo-1-alkenes prepared by Corey−Fuchs reaction may then be stereoselectively converted to di- or trisubstitued alkenes by selective halogen substitution reactions. *trans*-Selective monosubstitution was adequately developed by earlier workers, notably Tamao[118] and Roush,[119] while more demanding second substitution either with retention[120] or

with unexpected and nearly complete (≥97−98%) inversion[121] has been satisfactorily developed only recently by the authors' group, as detailed later. Perhaps more widely useful is to convert aldehydes to 1-alkynes. Once 1-alkynes are obtained, they may then be used as the starting compounds for alkyne elementometalation−Pd-catalyzed alkenylation. At present, base-induced elimination of 1,1-dihalo-1-alkenes obtained by Corey−Fuchs reaction[116] (eq 1, Scheme 23) and Ohira−Bestmann[122] modification of Seyferth−Gilbert carbonyl acetylenation[123] (eq 3, Scheme 23) are two of the most widely used protocols.

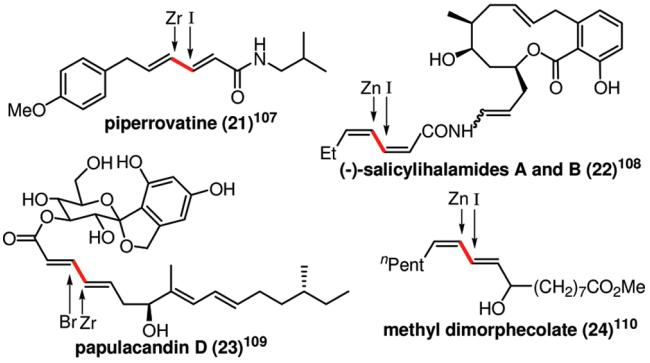
Aside from the synthesis of α-chiral 1-alkynes, 1-alkynes in general for use in alkyne elementometalation−Pd-catalyzed alkenylation are most widely accessible via none other than Pd-catalyzed alkynylation.[37] There are two discrete protocols, i.e., (1) Heck−Sonogashira alkynylation discovered in 1975,[36] of which the Cu-cocatalyzed Sonogashira version[36b] may have been more widely used, and (2) Negishi alkynylation discovered in 1977−1978[20,124] and its variants.[37] Although both are widely applicable and have indeed been widely applied, the currently available data indicate that the Heck−Sonogashira alkynylation is of considerably limited scope, as summarized below and that all of these difficulties can be readily overcome by using Negishi alkynylation (Scheme 24). It is important to note that free terminal alkynes (HC≡CR) are reactive in multiple and rather undisciplined manners, as compared with metalated derivatives (MC≡CR). Thus, ethyne is capable of reacting at both ends, and the second alkynylation tends to be faster (eq 1, Scheme 24). When substituted with electron-withdrawing groups, alkynes tend to react as electrophiles, e.g., Michael acceptors, etc. Furthermore, neutral alkynyl groups in free terminal alkynes are far more prone to homodimerization than MC≡CR.

Noteworthy in Scheme 24 is the use of (*E*)-1,2-iodobromoethene (**xvi**) in eq 6. As dicussed below, (*E*)-β-bromoenynes formed as the product can be subjected to the second Pd-catalyzed alkenylation to give a variety of enynes containing type III alkenyl groups.[126] Alternatively, they can be cleanly converted to 1,3-diynylmetals that can be further converted to various 1,3-diynes in a perfectly (100%) cross-selective manner[23b,128] (Scheme 25). For this purpose, however, (*E*)-1,2-iodochloroethene (**xvii**) may be preferable to **xvi**, even though both are satisfactory.

Of various conventional conjugated diyne syntheses, the Cu-catalyzed Cadiot−Chodkiewicz protocol[129] has been known for its applicability to the synthesis of unsymmetrical conjugated diynes. In reality, however, its cross-selectivity seldom is very high (≥98% or even ≥95%). Many attempts to develop highly (≥98%) cross-selective Pd-catalyzed alkynyl−alkynyl coupling procedures by the authors' group as well as by others have not yet been very successful, either. However, it now is practically feasible to achieve 100% cross-selective synthesis of a wide range of unsymmetrical conjugated diynes via Pd-catalyzed alkynyl−alkenyl coupling with roughly comparable efforts, as detailed in Scheme 26. Furthermore, the new enyne route can also be applied to highly efficient syntheses of conjugated oligoynes in a linear iterative manner (eq 1, Scheme 27), which can even be made partially convergent (eq 2, Scheme 27).[131] Unfortunately, these exciting

**SCHEME 21**

*1,4-Disubstituted 1,3-dienes via Negishi alkenylation*




*1,4-Disubstituted 1,3-dienes via Suzuki alkenylation*

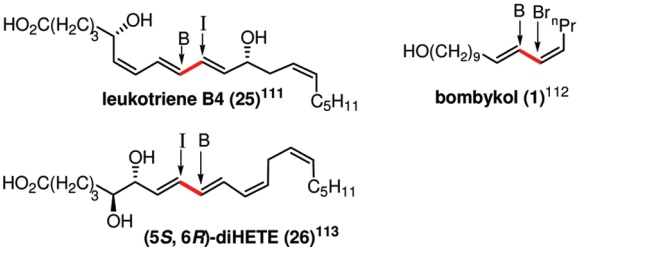
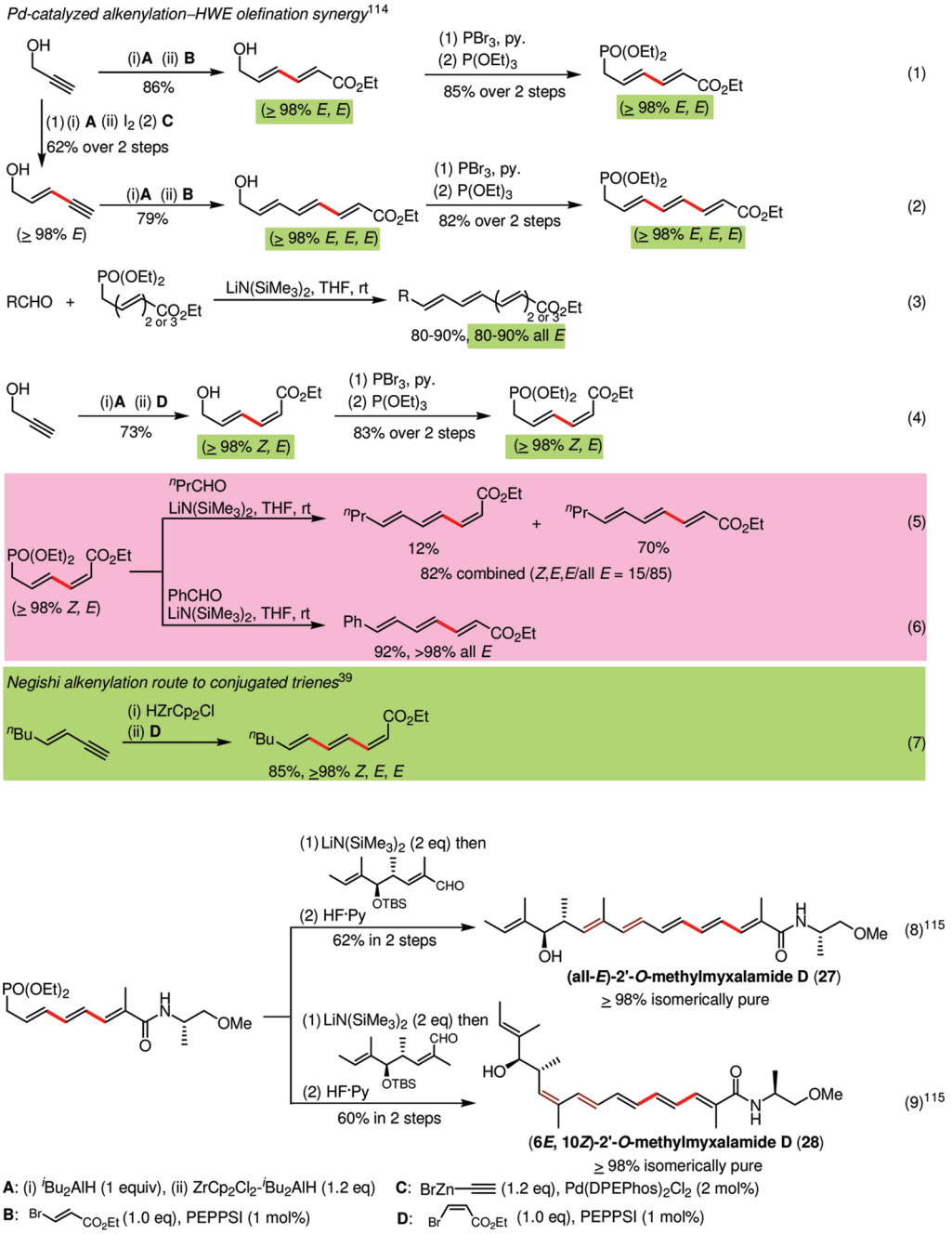



**TABLE 7. Current Scopes of the Conjugated Diene Syntheses by Negishi and Heck Alkenylations as Well as by HWE and SG&A Olefinations**

| Method | $R^1$ γ α $CO_2R$ δ β | δ γ $R^1$ α β $CO_2R$ | $R^1$ γ $CO_2R$ δ β α | δ γ $CO_2R$ $R^1$ β α |
|---|---|---|---|---|
| Pd-cat. cross-coupling (Negishi coupling with Zr or Zn) | • >80% yields<br>• ≥98% *E,E* | • >80% yields<br>• ≥98% *E,Z* | • >80% yields<br>• ≥98% *Z,E* | • >80% yields<br>• ≥98% *Z,Z* |
| Heck alkenylation | • use of either $H_2C$=$CHCO_2R$ or (*E*)-BrCH=$CHCO_2R$ can be high-yielding<br>• highly (≥98%) selective | • use of (*Z*)-$R^1$CH=CHX and $H_2C$=$CHCO_2R$ can be high-yielding<br>• ≥98% *E,Z* | • (*E*)-$R^1$CH=CHX + $H_2C$=$CHCO_2R$ not applicable.<br>• $R^1$CH=$CH_2$ and (*Z*)-BrC=$CHCO_2R$ not highly stereoselective (<95%) and widely variable. | • not applicable |
| HWE olefination (Horner-Wadsworth-Emmons olefination) | • widely applicable<br>• high-yielding<br>• stereoselectivity varies over a wide range<br>• typically ≤90% *E,E* unless $R^1$ favors the *E,E* isomer, e.g., Ph | • high-yielding<br>• synthesis of (*Z*)-$R^1$CH=CHCHO can be cumbersome | • generally not applicable<br>• use SG&A alkenylation | • generally not applicable<br>• use SG&A alkenylation |
| SG&A olefination (Still-Gennari and Ando olefination) | • generally not applicable<br>• use HWE olefination | • generally not applicable<br>• use HWE olefination | • can be high-yielding and highly (>98%) selective<br>• see Eq. 5 in Scheme 20 | • not stereoselective (Eqs. 6 and 7, Scheme 20) |

**SCHEME 22**




conjugated oligo- and polyynes have been reported to potentially explosive.[132] For this reason, efforts in the authors' group were prematurely terminated, but shorter oligoynes are known to exhibit interesting biological activities, including antibacterial, antifungal, antiinflammatory, antiangiogenic, antimicrobial, cytotoxic, and larvicidal activities,[133] and their syntheses in the y(es)$^2$ manner, as shown in Schemes 26 and 27, promise to facilitate studies in these areas.

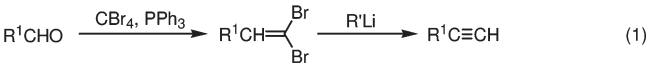
Although no detailed discussion is intended, conjugated enynes can serve as useful precursors to conjugated dienes containing type IV alkenyl groups. The alkyne hydroboration–protonolysis protocol of Zweifel[18b] has been applied to the stereoselective syntheses of symmetrical (*Z*,*Z*)-1,3-dienes[18b] and unsymmetrical (*E*,*Z*)-1,3-dienes[16b,c] (Scheme 2). With the development of 100% cross-selective route to conjugated diynes, a wide range of unsymmetrical conjugated (*Z*,*Z*)-dienes should be accessible in the y(es)$^2$ manner. Perhaps more attractive and satisfactory is to further develop transition metal-catalyzed selective partial hydrogenation of conjugated enynes and diynes in the y(es)$^2$ manner.

It goes without saying that conjugated enynes themselves represent a very important class of natural products, and the Pd-catalyzed alkynyl–alkenyl and alkenyl–alkynyl coupling reactions have provided highly satisfactory routes to them in the y(es)$^2$ manner, as exemplified in Schemes 15 and 28.

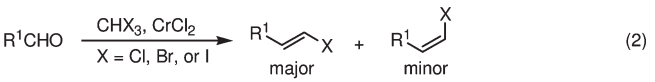
**(2) Conjugated Dienes, Enynes, and Their Oligomeric Homologues Containing One or More Trisubstituted Alkenes.** Trisubstituted alkenes are either *E* or *Z*. Although a wide

**SCHEME 23**

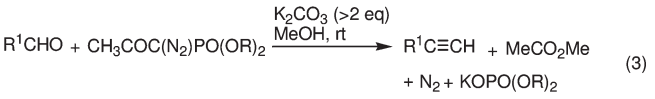
*Corey-Fuchs reaction*[116]




*Takai reaction*[117]




*Ohira-Bestmann acetylenation*[122]

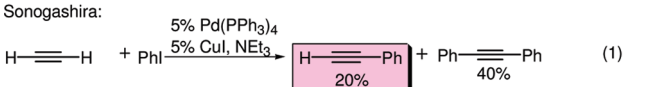



**SCHEME 24**

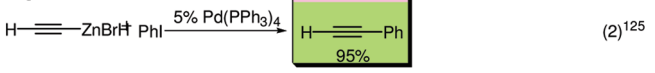
*Sonogashira alkynylation vs. Negishi alkynylation*

*(a) one-step synthesis of terminal alkynes*

Sonogashira:

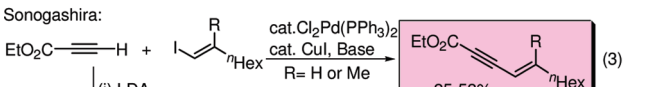



Negishi:

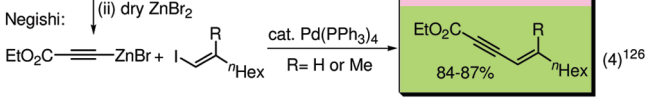



*(b) electron withdrawing group-containing alkynes*

Sonogashira:



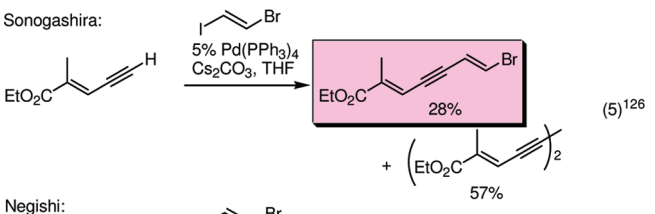

Negishi:



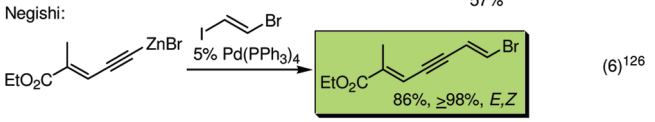

**Note:** $EtO_2C{-}{\equiv}{-}H$ is a good Michael acceptor.

*(c) use of*  **(xvi)**

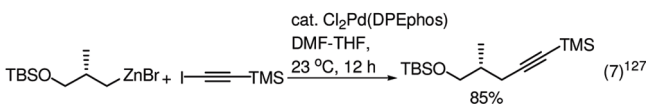
Sonogashira:




Negishi:

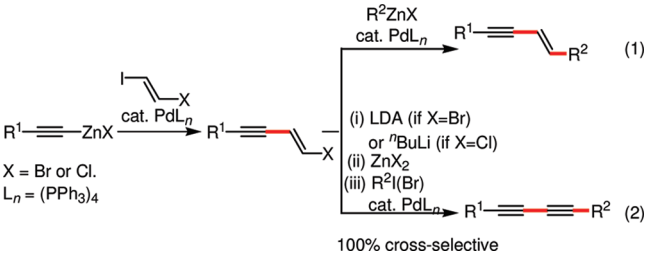



*(d) use of haloalkynes: not an available option with the Heck-Sonogashira protocol*




variety of synthetic methods are available, the conventional *carbonyl olefination* and the modern *Pd-catalyzed alkenylation* appear to be the two representative and widely applicable methods. At present, the former is indispensable for accommodating chiral groups α to C=C bonds. Aside from this critically important aspect, the Pd-catalyzed alkenylation methodology as a whole is comparatively even more advantageous than in the cases of disubstituted alkene synthesis detailed in the preceding section, especially in terms

**SCHEME 25**




of stereochemical control (≥98%). In cases where carbonyl olefination reactions satisfy the y(es)[2] factors, however, they should and will be considered and used.

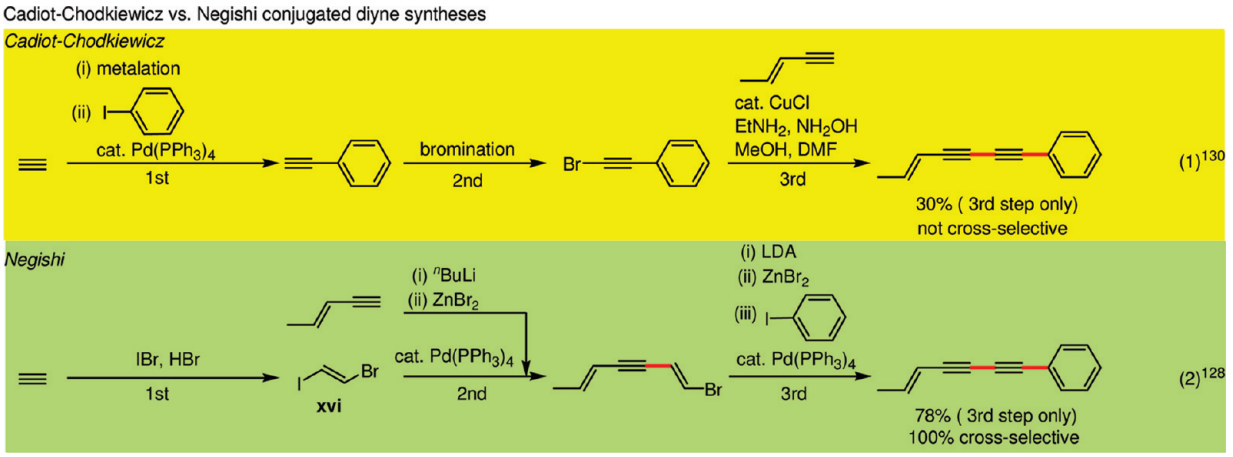
Of the four types of alkenyl groups highlighted in yellow in Table 4, type V and VI alkenyl reagents may be used for preparing either *E*- or *Z*-trisubstituted alkenes in the tail-to-head (**T**-to-**H**) manner, whereas the stereochemical outcome in their syntheses via type VII and VIII alkenyl reagents are preset in essentially all known cases. As a brief reminder, the following summary (Table 8) is presented, and this summary should also be supplemented with pertinent information presented in Scheme 16.

Most of the reactions indicated in Table 8 were discussed in some specific details, but a brief discussion of the widely used *syn*-carbometalation of 1-alkynes is in order at this point.

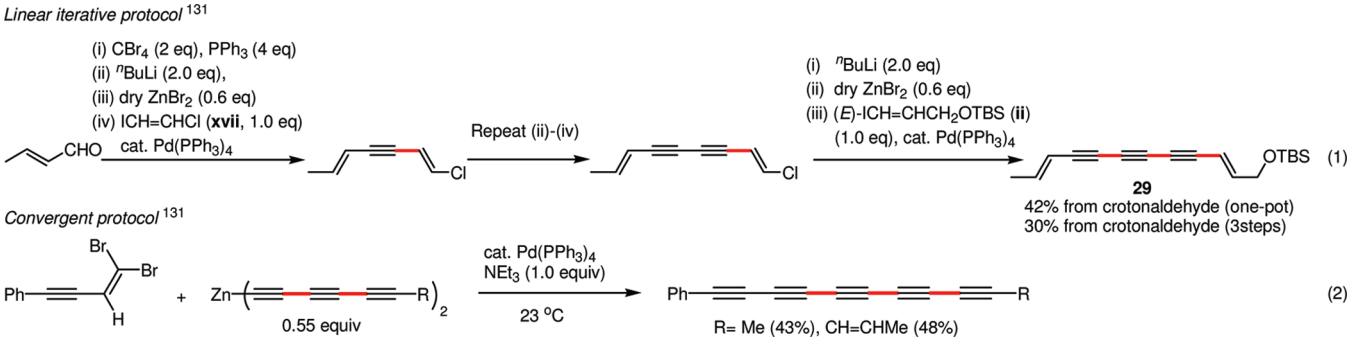
**(a) Zr-Catalyzed Methylalumination of Alkynes (ZMA Reaction) and Related Reactions.** The Zr-catalyzed methylalumination of alkynes (ZMA reaction) discovered in 1978[63] is a genuine bimetallic process requiring both Zr and Al at the crucial moment of carbometalation[64,136] (manifestation of the "two is better than one principle"[137]). The reaction is broad in scope with respect to $R^1$ in the single-most important case of methylalumination. Some other organoaluminum compounds, such as those containing benzyl and allyl, react similarly. Although many other alkylaluminiums also undergo Zr-catalyzed reactions with alkynes, triisoalkylalanes, e.g., $^{i}Bu_3Al$, undergo β-H-transfer hydroalumination under otherwise the same conditions,[59] while ethyl- and *n*-alkyl-containing alanes undergo mechanistically highly intriguing Zr-catalyzed cyclic carboalumination.[65,138] Both of these reactions must be attributable to favorable β-agostic interaction of alkylzirconium species. It is clearly desirable to overcome these difficulties. In the meantime, however, the ZMA reaction has been applied to the stereoselective syntheses of well over 150 natural products and related compounds as of 2006.[3b] Some critical aspects of the ZMA reaction are summarized in Scheme 29, and the Pd-catalyzed alkenylations with the alkenylalanes are discussed below.

**(b) Alkylcupration.** The ZMA reaction and alkylcupration are complementary in that ethyl and higher unhindered alkylcupration proceed readily, although methylcupration is sluggish.[61,139] While the products of alkylcupration of ethyne (type IV) have been used in their Pd-catalyzed alkenylation,[6] the corresponding reactions of the type VII and VIII alkenylcoppers do not appear to have been adequately investigated. Even so, once the alkenylcoppers are converted to alkenyl halides and other derivatives, they will serve as useful type VII and VIII alkenyl regents.

**SCHEME 26**



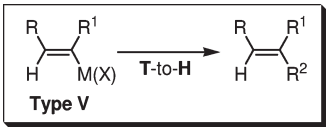

**SCHEME 27**




(c) **Haloboration.** In view of the brief discussion of the current scope and limitations of alkyne carbometalation presented above, recent development of the alkyne bromoboration–Pd-catalyzed alkenylation protocol, especially those involving the use of propyne[73a] and arylethynes[73b] highlighted earlier and summarized in Scheme 9, represents a significant breakthrough in the selective syntheses of type VII and VIII alkenyl derivatives.

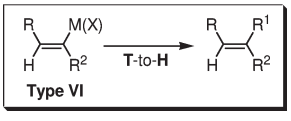
It goes without saying that any additional methods and procedures that satisfy the y(es)[2] criteria would contribute to further development of Pd-catalyzed alkenylation methodology. Although somewhat more specialized, those routes to types V–VIII alkenyl reagents based on hydrometalation (Schemes 8, 10, 11, and 14) and proximal heteroatom-guided carbometalation reactions (Schemes 13 and 14) along with those reagents shown in Scheme 16 have firmly established themselves as important and indispensable parts of the Pd-catalyzed alkenylation methodology.

**Applications of Type V–VIII Alkenyl Reagents to the Synthesis of Natural Products Containing Conjugated Di- And Oligoenes. (i) Type V Alkenyl Derivatives.**




As indicated in Table 8, type V alkenyl derivatives are most widely and stereoselectively prepared by *syn*-hydrometalation of internal alkynes. One generally observed problem is that with internal alkynes with two carbon substituents ($R^1C{\equiv}CR^2$), the reaction may be of low regioselectivety, unless the two carbon groups are markedly dissimilar. In this respect, hydrozirconation displays two features leading to high regioselectivity levels. One is its ability to undergo facile regioisomerization in the presence of an excess of $HZrCp_2Cl$, and the other is the conversion of proximally *O*-substituted internal alkynes having a Me group at the other end of the C≡C group with in situ generated $HZrCp_2Cl$+$^t Bu_2AlCl$·THF (reagent I) (eq 6, Scheme 8). Although limited in scope, these special cases have proven to be of considerable usefulness, as demonstrated in the synthesis of reveromycin B[140] and motuporin[141] (Scheme 30). More dependable and widely applicable is to resort to *syn*-hydroboration of 1-halo-1-alkynes followed by Pd-catalyzed Negishi coupling (eq 3, Scheme 10). Following a promising lead provided by Suzuki,[79] this new protocol has been developed in the authors' group,[75] and it promises to provide a widely applicable route to type V alkenyl derivatives.

**(ii) Type VI Alkenyl Derivatives.**



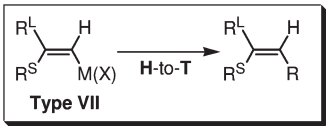

As shown in Scheme 14, *anti*-hydroalumination of propargylic alcohols provides two kinds of type VI alkenylaluminum derivatives that can be readily converted to the corresponding iodides of ≥98% *Z* geometry,[86,87] and they have been used for the synthesis of various natural products of

**TABLE 8. Summary of Elementometalation Route to Types V−VIII Alkenyl Reagents**

| Elementometalation | Type V | Type VI | Type VII | Type VIII |
|---|---|---|---|---|
| *syn*-Hydrometalation of R¹—≡—R | Yes (Scheme 8, limited) | — | — | — |
| *syn*-Hydrometalation of R¹—≡—X | Yes (Scheme 10) | Yes (Scheme 10) | — | — |
| *syn*-Hydrometalation of R¹—≡—M' | Yes | Yes (Scheme 11) | — | — |
| *anti*-Hydrometalation of R¹—≡—OH | — | Yes (Scheme 14) | Yes (Scheme 14) | Yes (Scheme 14) |
| *syn*-Carbometalation of R¹—≡—H | — | — | Yes (Scheme 29) | Yes (Scheme 29) |
| *syn*-Carbometalation of H—≡—OH | — | — | Yes (Scheme 13) | Yes (Scheme 13) |
| *anti*-Carbometalation of R¹(H)—≡—OH | — | — | Yes (Scheme 14) | Yes (Scheme 14) |
| *syn*-Halometalation of R¹—≡—H | — | — | Yes (Scheme 9) | Yes (Scheme 9) |

terpenoid origin. Potentially more general is the 1-halo-1-alkyne hydroboration−migratory insertion route to type VI alkenylboranes[77,78] (Scheme 10). Although their Pd-catalyzed Suzuki coupling had been problematic,[78] their in situ transmetalation to the corresponding Zn derivatives have been shown to readily undergo highly demanding type VI−type IV and even type VI−type VIII alkenyl−alkenyl coupling, as exemplified by the synthesis of potential intermediates for callystatin A[142] and archazolid A or B[143,144] (Scheme 31). More recently, a simple and highly satisfactory procedure for direct Suzuki coupling has also been developed in the authors' group, which promises to provide an ultimately satisfactory 1-halo-1-alkyne bromoboration−Negishi−Suzuki coupling tandem protocol.[75]

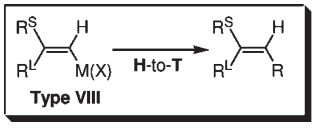
**(iii) Type VII Alkenyl Derivatives.**




A highly (≥98%) stereoselective synthesis of vitamin A[145,146] via alkyne ZMA−Pd-catalyzed alkenylation protocol (eq 1, Scheme 32) was followed by exceedingly efficient and selective synthesis of $\beta$- and $\gamma$-carotenes[146] (eqs 2 and 3, Scheme 32). In the latter, the use of (*E*)-ICH=CHBr (**xvi**) as a 2C linchpin should be noted. Although no rigorous comparisons were attempted, the overall superiority of the Pd-catalyzed alkenylation route over the conventional carbonyl olefination route[147] appears to be rather clear.

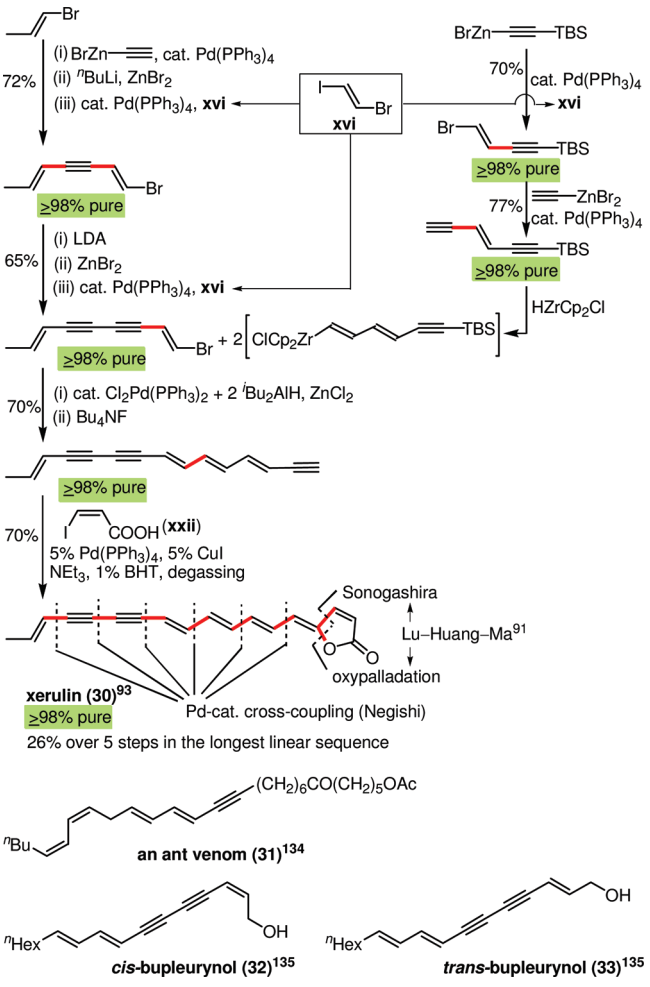
Shown in Scheme 33 are just a few representative examples of the preparation and application of Type VII alkenyl derivatives via ZMA reaction for the synthesis of conjugated di- and oligoenes.[148−152] Those examples shown in eqs 1 and 2 in Scheme 33 demonstrate the use of 1,4-pentenyne for both ZMA and ZACA reactions in efficient and selective terpenoid syntheses.[151,152]

**(iv) Type VIII Alkenyl Derivatives.**




Some of the basic results of the alkyne bromoboration−Pd-catalyzed alkenylation protocol were presented in Scheme 9. Its applications to some natural products syntheses are shown in Scheme 34.

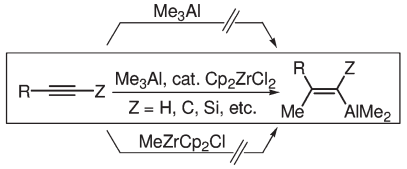
**SCHEME 28**



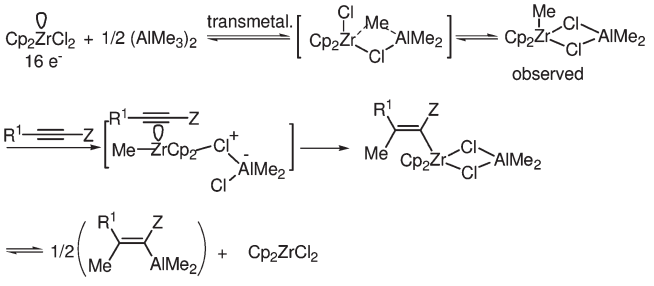

In addition to the alkyne elementometalation routes to type V−VIII alkenyl derivatives, some highly selective alkyne polar addition routes to type V−VIII alkenyl derivatives, such as **xviii**, **xix**, **xxiii**, and **xxv** shown in Scheme 16, along with many other type III and IV alkenyl derivatives, have been shown to be synthetically useful, and their applications are

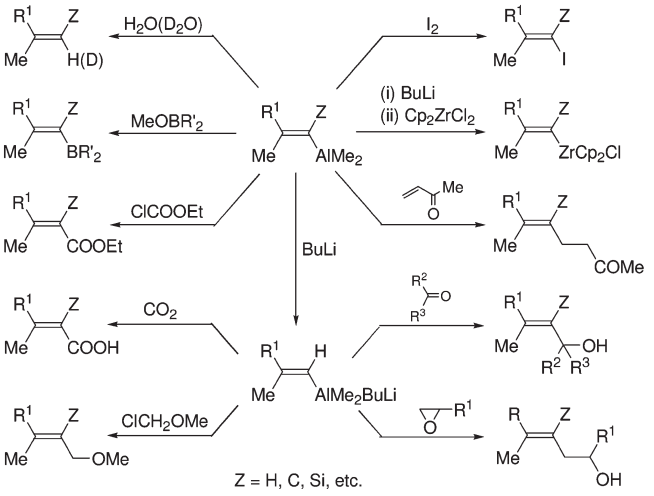
**SCHEME 29**

*Zr-catalyzed methylalumination of alkynes (ZMA)*[63]




*proposed machanism*[64]



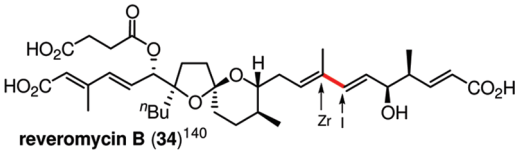



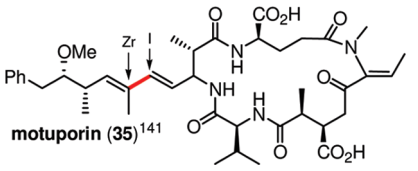

shown throughout this paper. Applications of some of the less widely used ones are summarized in Scheme 35.

**Unexpected Stereoisomerization and Its Prevention in the Pd-Catalyzed Double Substitution of 1,1-Dihalo-1-alkenes.** *"Be aware of capricious allylics! Tame them or avoid them."* Ni- or Pd-catalyzed monosubstitution of 1,1-dihalo-1-alkenes was shown to exhibit surprisingly high (≥98%) *trans*-stereoselectivity, if a sufficient excess of an organometallic reagent is used to selectively convert the minor *cis*-monosubstitution product with the faster reacting *trans*-halogen atom.[118,119] This selective monosubstitution has been used widely, notably by Roush,[119] for natural product synthesis. Progress in the development of the second substitution was sluggish until a high-yielding and stereoselective reaction proceeding with surprising and nearly full (≥97−98%) stereoinversion[121] was discovered (Scheme 36). It was soon found that the use of highly active Pd catalysts, such as $Pd(^tBu_3P)_2$ and $Pd_2(dba)_3$ used in conjunction with *N*-heterocyclic carbenes (NHCs),[155] would almost completely (≥98%) suppress stereoinversion mentioned above.[120] Thus, other stereoisomers may now be obtained as ≥97−98% pure conjugated dienes.

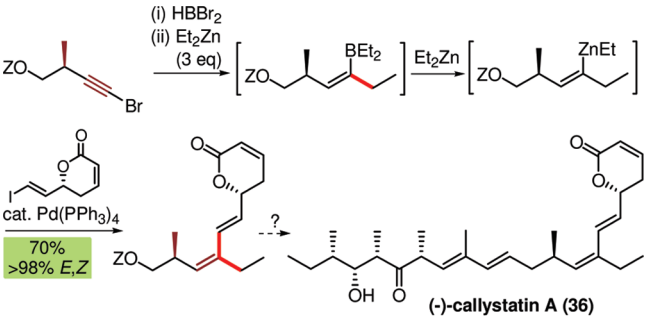
**SCHEME 30**

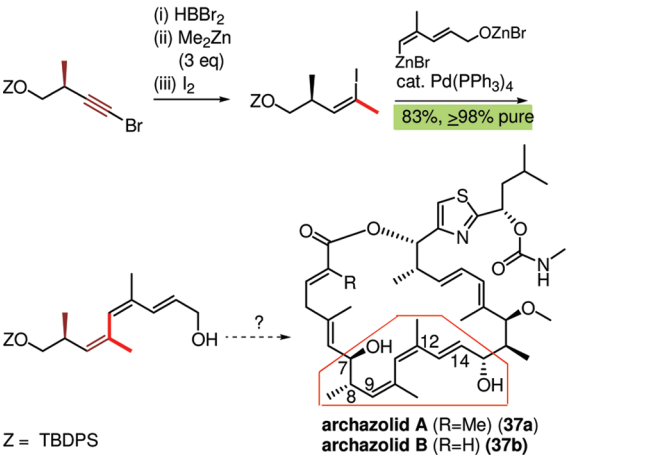
*Type V alkenyl derivatives via hydrozirconation*




**SCHEME 31**

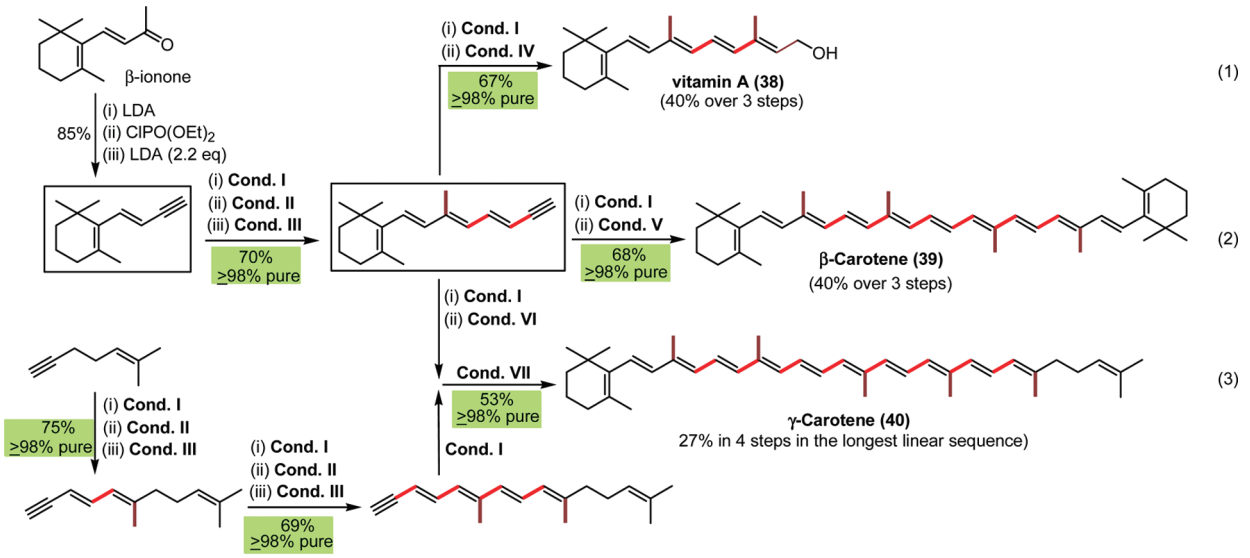



Although precise mechanistic details are still under investigation, 2-bromo 1,3-dienes (**51**) are simultaneously alkenylic and allylic. Their bulky $PdL_n$-containing derivatives must possess strong desire to acquire the *trans*-alkenyl geometry (R′ and Pd being *trans* to each other) on one hand and a good opportunity to do so through reversible allylic rearrangement with inversion. In the second substitution of alkynylated, partial isomerization occurs,[121] while the extent of isomerization with arylated derivatives is ≤5%. It should also be noted that, as anticipated, the use of unsaturated groups as $R^1$ can almost completely suppress the stereoisomerization.[121]

It is gratifying to learn that both processes, one with inversion (eq 4, Scheme 36) and the other with retention (eq 5, Scheme 36), have been satisfactorily applied to the syntheses of complex natural products (Scheme 37).

**SCHEME 32**[a]




[a]Note: Roman numerals represent a series of operations within a step.

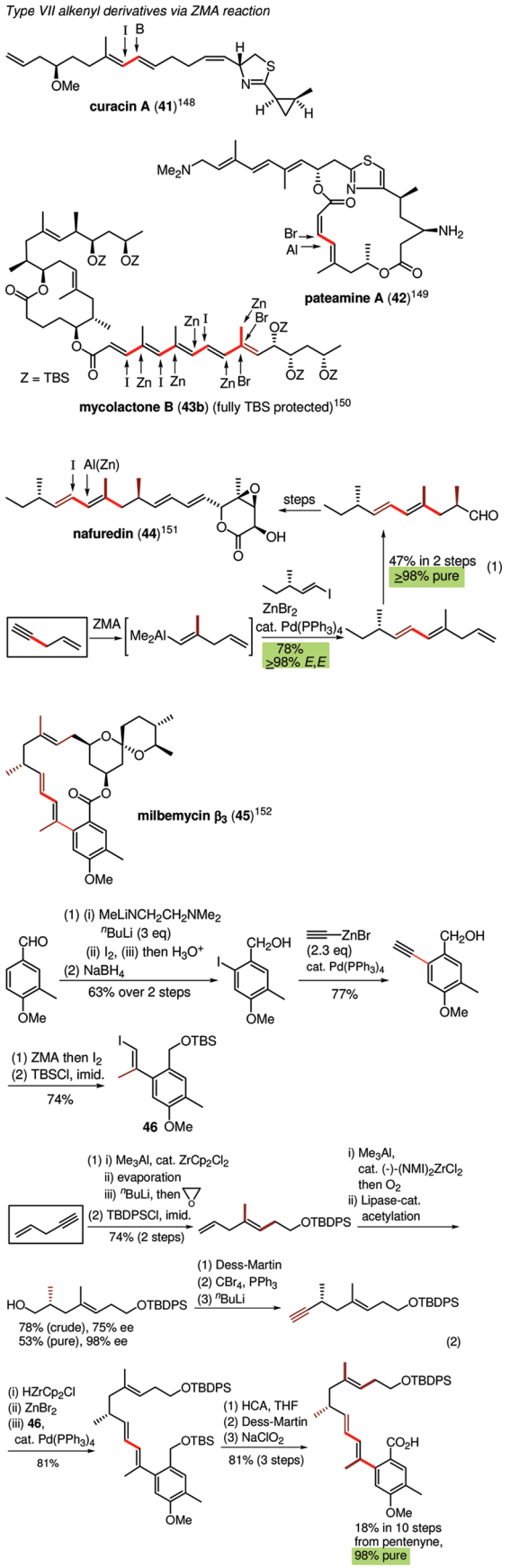
One of the widely observed limitations in Pd-catalyzed selective substitution of 1,1-dihalo-1-alkenes has been the difficulty in selectively effecting the first *trans*-selective substitution with an alkyl group. Although this still remains as an important challenge, the first monoalkylation of 1,1-dichloro-1-alkenes with alkylzincs of both RZnX- (X = Cl, Br, etc.) and $R_2Zn$-type including $Me_2Zn$ in DMF in the presence of catalytic amounts of $Cl_2Pd(DPEphos)$ has been shown to proceed well to give the desired ≥98% isomerically pure *trans*-monoalkylated products in 70−90% yields. The second substitution also proceeds in high yields with organomagnesiums containing alkyl, aryl, alkenyl, and allyl groups through the use of highly active catalysts, such as $Pd(Cy_3P)_2$[162] (eq 1, Scheme 38). *trans*-Selective monoalkylation can proceed well even with 1,1-dibromo-1-alkenes containing certain favorable substituents, such as the conjugated $Me_3SiC{\equiv}C$ group[150b] (eq 2, Scheme 38). It is anticipated that this reaction may be further developed through reaction parameter optimization. It should also be noted that lithiation at −110 °C with $^t$BuLi (2 equiv) of a 2-bromo-1,3-diene derivative shown in eq 3, Scheme 38, followed by treatment with $CO_2$ proceeded with full retention of configuration to give the desired carboxylic acid, which was subsequently converted to an antibiotic, lissoclinolide synthesized in 32% overall yield in nine steps from propargyl alcohol.[163]

**(3) 1,4-Dienes via Pd-Catalyzed Alkenyl−Allyl and Allyl−Alkenyl Coupling and 1,4-Enynes via Pd-Catalyzed Alkynyl−Allyl Coupling.** Allylic or propargylic organometals containing a coordinatively unsaturated metal can readily undergo facile allyl or propargyl−allenyl rearrangement. In many cases, they may even be considered as resonance hybrids. After all, these rearrangements are nothing more than intramolecular carbometalation processes. As might be predicted from the simple reasoning presented above, the reactions of allylic halides and related derivatives should be more likely to proceed with retention of allylic structural integrity than the corresponding reactions of allylmetals. This generalization has been repeatedly supported by experimental observations.

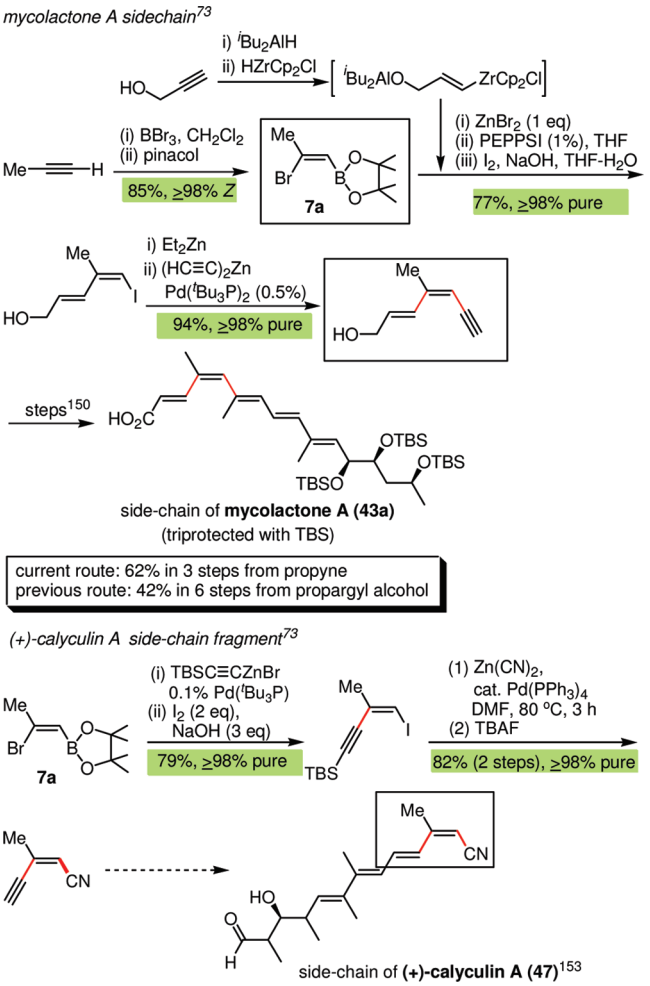
One of the earliest demonstrations of Pd-catalyzed allylation with ≥98% stereoretention was one-step synthesis of (*E*)- and (*Z*)-α-farnesenes in ≥98% selectivety (eqs 1 and 2, Scheme 39).[22a] However, these cases are aided by the fact that geranyl and neryl chlorides are γ,γ-disubstituted allylic derivatives. With γ-monosubstituted allylic derivatives, full stereo- and regiochemical retention has been generally difficult, both stereo- and regio-scrambling occurring typically to the extents of roughly up to 10% (eq 3, Scheme 39).[22c] Nevertheless, it has recently been found that, if the γ-substituent is bulky, e.g., secondary alkyl, clean allylation may be observed (eq 4, Scheme 39).[150b] This favorable δ-branching effect was profitably exploited in recent synthesis of mycolactone core (eq 5).[150b] Although finer details are not clear, applications of the Pd-catalyzed alkenyl−allyl coupling involving the use of B[164] and Sn[165] shown in Scheme 39 further demonstrate synthetic utility of this reaction.

With allylmetals as reagents, the Pd-catalyzed allyl−alkenyl coupling appears to generally produce thermodynamically equilibrated mixtures (eq 1, Scheme 40). Nonetheless, in cases when no isomerization is possible, such as allylation with the parent allyl, 2-substituted allyl, and symmetrically γ,γ-disubstituted allyl derivatives, it offers a useful alternative, especially when the complementary alkenyl−allyl coupling is not a viable option, as in the highly efficient and selective synthesis of yellow scale pheromone (**61**) (eq 2, Scheme 40).[72]

**SCHEME 33**



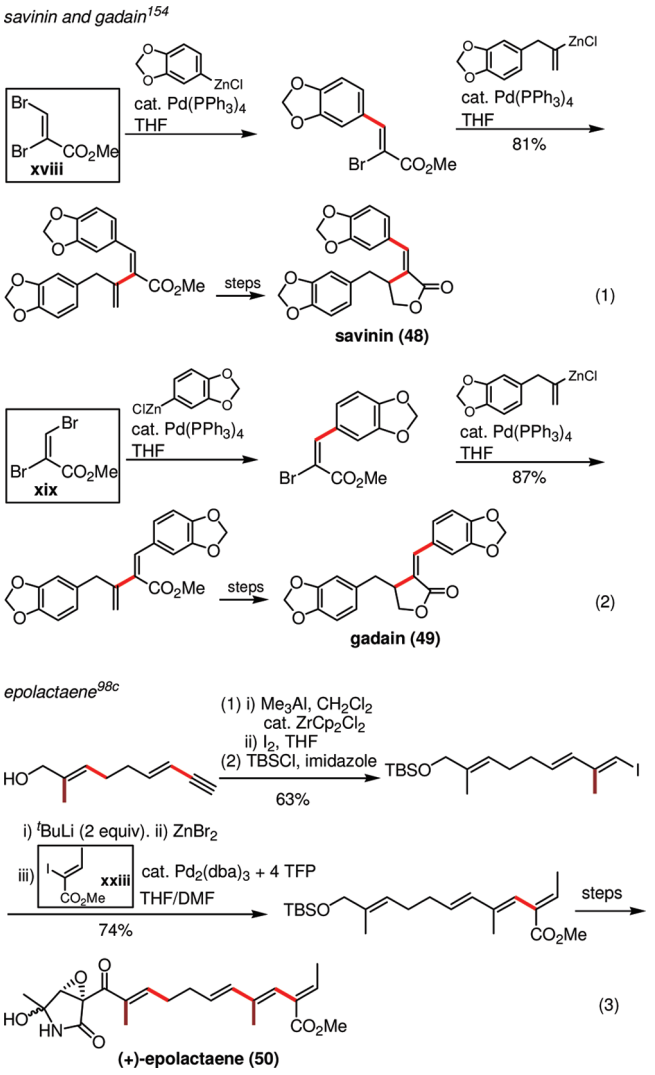

**SCHEME 34**




Little, if any, was known until recently about the Pd-catalyzed alkynyl−allyl coupling. Indeed, this reaction has turned out to be rather difficult and highly demanding. Even so, a recent study[166] indicates that highly (≥98%) stereoselective results highlighted in green in Table 9 may be obtained, provided that alkynylzinc derivatives are reacted with geranyl or neryl chloride or acetate, the former being preferable, in the presence of 1 mol % of a Pd catalyst in 1:1 THF−DMF. Indium, which has been shown to be one of the two other highly satisfactory countercation for the Pd-catalyzed alkynyl−benzyl coupling along with B,[167] is only marginally satisfactory. Furthermore, none of these metal countercations, Zn, In, and B, can maintain very high (≥98%) stereoselectivity levels with 0.1 mol % of Pd(DPEphos)$Cl_2$, one of the only two satisfactory catalysts along with Pd(dppf)-$Cl_2$ among those screened for alkynyl−benzyl coupling.[167] Further development is clearly desirable.

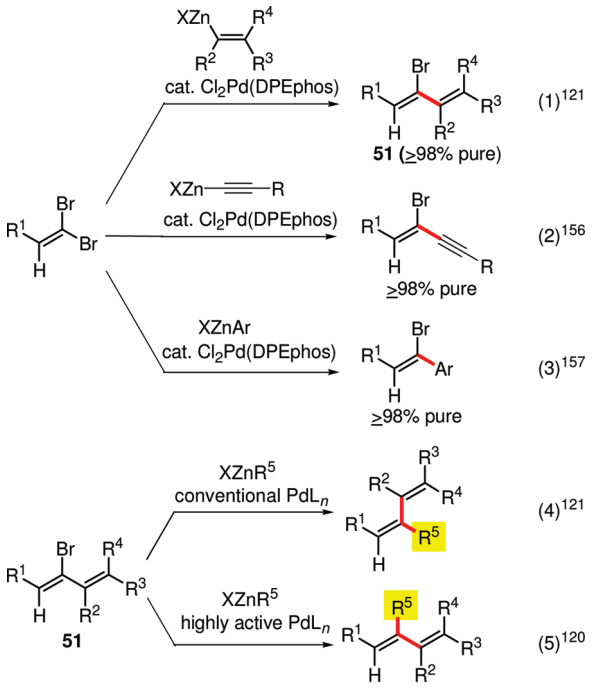
Although not discussed in detail here, Pd-catalyzed propargylation has a strong tendency to produce allenes.[168] Even so, some favorable examples of propargylation are also known, as shown in Scheme 41.[169] It should also be reminded that allylation and propargylation as well as benzylation proceed well with Cu catalysts or even without any transition-metal catalysts in many cases and that any Pd-catalyzed reaction must be competitively and objectively compared with them for optimal choices.

**SCHEME 35**




**(4) 1,5-Dienes and 1,5-Enynes via Pd-Catalyzed Homoallyl−Alkenyl Coupling and Homopropargyl−Alkenyl Coupling.** 1,5-Dienes represent a large number of biologically important natural products of terpenoid origin and many others. Their highly (≥98%) selective synthesis before the advent of Pd-catalyzed cross-coupling was very difficult and tedious. One of the most satisfactory procedures, widely known as Biellmann coupling,[170] involves controlled allyl−allyl coupling for which naturally occurring and structurally defined isoprenoids, such as geraniol, are to be suitably functionalized at one or the other end. Just to link two isoprenoid segments, it takes several steps, and removal of the activating heteroatom groups, e.g., sulfur groups, is usually accompanied by partial isomerization (~10%). This several-step process must be repeated for the synthesis of higher oligomers. Construction of (*Z*)-isoprenoids is generally even more demanding and problematic.[171] Unfortunately, alternate alkenyl−homoallyl and/or homoallyl−alkenyl coupling reactions were not viable options before the discovery of Pd- or Ni-catalyzed cross-couplings, since homoallyl electrophiles are highly prone to *β*-elimination and since essentially no known and satisfactory homoallyl−alkenyl coupling procedure had been available, until a surprisingly selective and high-yielding (80−90%) Pd-

**SCHEME 36**

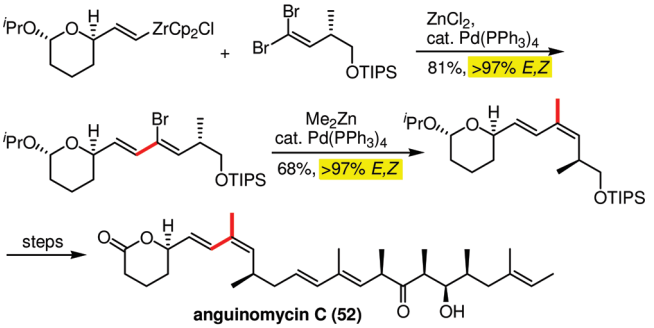



catalyzed homoallyl−alkenyl and homopropargyl−alkenyl coupling procedures using homoallyl- and homopropargylzincs was discovered in 1980.[21a] As expected, this reaction is highly general with respect to the structure of alkylzincs[21a,172] ($R^1ZnX$ and $R^1{}_2Zn$), as long as $R^1$ is Me and primary alkyl including isoalkyl. Even secondary alkyls may also be used, but their absolute configuration, if any, will be at least partially lost, unless asymmetrically maintained externally and/or internally.[40] Several years later, a related alkylboron reaction was also developed by Suzuki[173,174] and has become widely used along with the Zn version. Even Grignard reagents and other organomagnesiums may also be used in cases where *β*-elimination and other chemoselectivity issues are absent or insignificant.[8f,21a,172] Although alkyltins have also been used,[5] they are usually not sufficiently reactive with possible exception of methyltins, besides being associated with other procedural and toxicity-related difficulties. From the latter perspective, Si[10] may be more promising despite its inherently low reactivity. Perhaps more promising are less frequently used alkylmetals containing Al and Zr. In view of their ready availability via hydroalumination, hydrozirconation, and Zr-catalyzed carboalumination (ZACA),[3b,175−177] promotion of Pd-catalyzed alkylation with these metals clearly deserves to be further explored. Indeed, a ZACA−Pd-catalyzed cross-coupling tandem process using $Zn(OTf)_2$ as a promoter and DMF as solvent permitting *"one-step" homologation of deoxypolypropionate by one propylene unit* was recently developed[178] (Scheme 42).

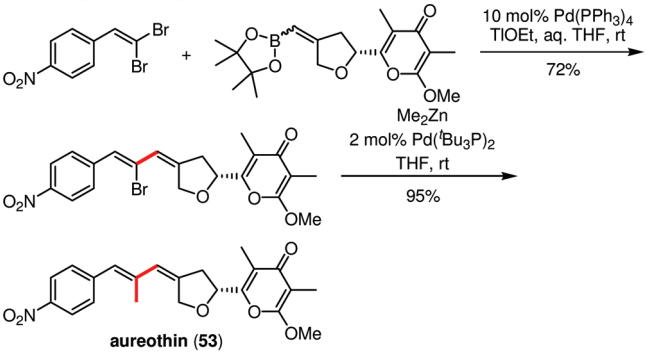
In recent syntheses of coenzymes $Q_n$ (**63**, $n \geq 3$) and menaquinones-*n* (**64**, $n \geq 3$), their final assembly has been most efficiently performed by resorting to either Pd-[179] or

**SCHEME 37**

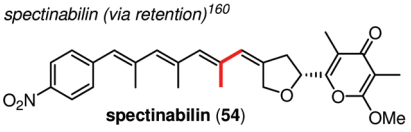
*anguinomycin C (via inversion)*[158]



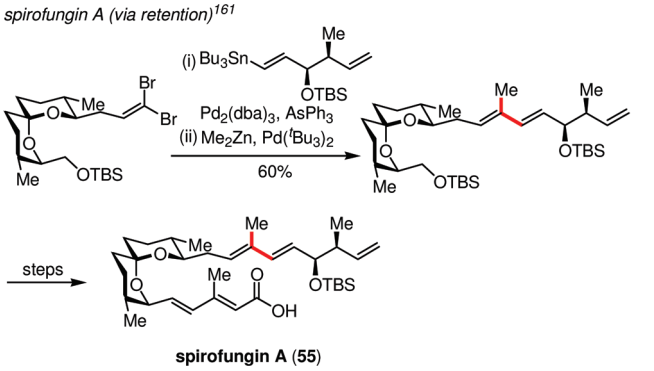

*aureothin (via retention)*[159]




*spectinabilin (via retention)*[160]




*spirofungin A (via retention)*[161]

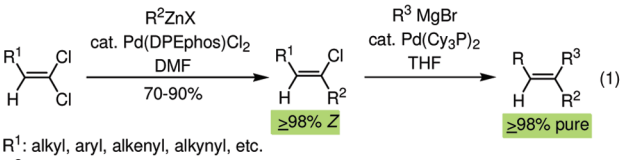



Ni-catalyzed[180] alkenylation of the corresponding chloromethylquinones with (*E*)-*β*,*β*-disubstitued alkenylaluminums generated in situ by ZMA reaction. Both Pd and Ni catalysts have been reported to be highly satisfactory, and their comparative overall merits are still to be further evaluated with all of the y(es)$^2$ factors in mind (Scheme 43).

For highly efficient and selective syntheses of 1,5-diene-containing terpenoidal side chains, the following findings and developments were critically important: (i) syntheses of strategically structured *E* and *Z* isomers of 1,4-diiodo-2-methyl-1-butene (**viii** and **x**) in the y(es)$^2$ manner in two steps from 3-butyn-1-ol, as shown in Scheme 13,[21c,85,179] (ii) exclusive (> 500/1) substitution at C1 in the Pd-catalyzed

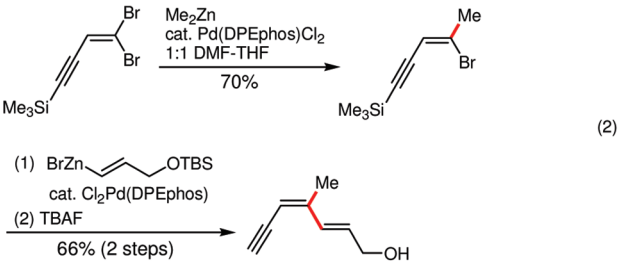
**SCHEME 38**

*trans-monoalkylation of 1,1-dichloro-1-alkenes*[162]

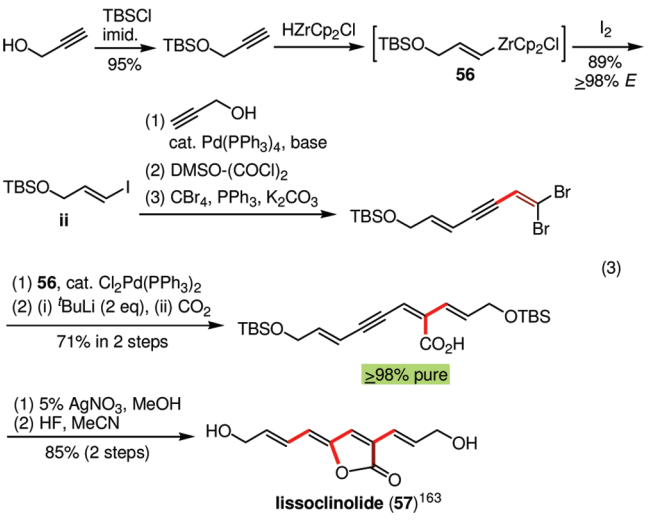



$R^1$: alkyl, aryl, alkenyl, alkynyl, etc.
$R^2$ZnX: $Me_2Zn$ (NMI), $Et_2Zn$, $^n$OctZnBr, $^n$OctCH(Me)$CH_2$ZnBr
$R^3$: alkyl, aryl, alkenyl, but not alkynyl

*trans-monomethylation of 1,1-dibromo-4-trimethylsilylbut-1-en-3-yne*[150b]




*efficient and selective syntehsis of lissoclinolide*[163]




cross-coupling of **viii** and **x**,[21c,179] and (iii) very fast and clean lithiation of primary alkyl iodides via Li−halogen exchange in essentially quantitative yields at or below −78 °C, which is observable only if (a) $^t$BuLi (2 equiv), (b) primary (normal and iso) alkyls, (c) iodides (not bromides), and (d) ether (not THF, etc.) are used.[181]

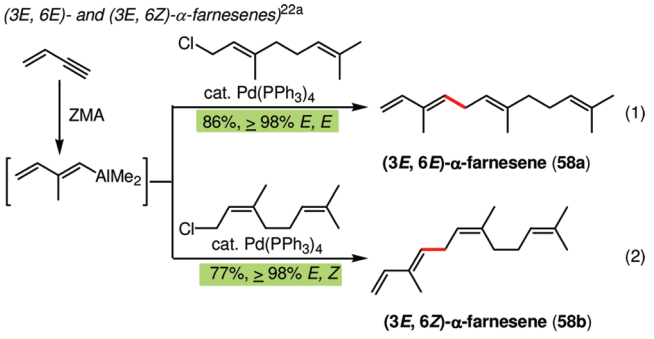
Under these conditions, no side reactions, such as homodimerization, *β*-elimination (−H), deiodination (protonolysis), etc., were detectable (< 1%).

A wide variety of 1,5-diene-containing acyclic isoprenoids are now preparable in one step or less per one isoprene unit in > 99% *E* and ca. 98% *Z* selectivity, as shown in Scheme 43.

**(5) Pd-Catalyzed α-Alkenylation, α-Arylation, and α-Alkynylation of α-Halo- and α-Metallo-α,*β*-unsaturated Enones.** Substitution of ketones and other carbonyl compounds in their α-positions via enolate alkylation is a fundamentally important transformation. And yet, it has remained even today as a limited and capricious synthetic operation, despite some significant recent developments, especially with

**SCHEME 39**

*(3E, 6E)- and (3E, 6Z)-α-farnesenes*[22a]




*use of γ-monosubstituted allyl derivatives*[150b]

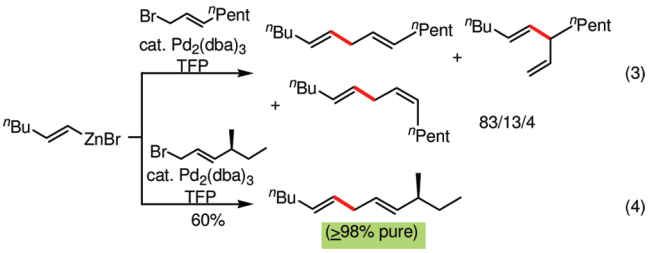
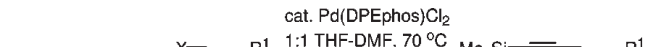
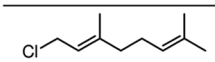
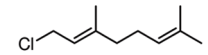
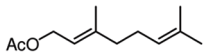
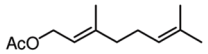
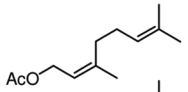
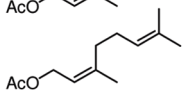



**TABLE 9. Effects of Palladium Catalyst Loading on the Stereoselectivity of the Reaction of $Me_3SiC{\equiv}CML_n$ with Geranyl and Neryl Electrophiles in the Presence of Pd(DPEphos)$Cl_2$**[166]

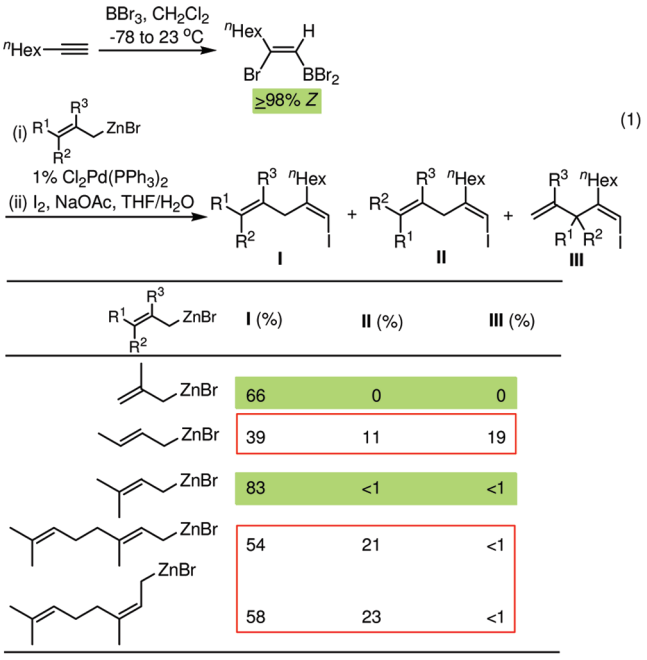



| $XCH_2CH{=}CR^1R^2$ | catalyst loading (mol%) | time (h) | $ML_n$[a] | yield of *E* and *Z* isomers (%)[b] | *E*/*Z* |
|---|---|---|---|---|---|
|  | 1.0 | 4 | ZnBr | 91 | 98.5/1.5 |
| | | | In(C≡CSiMe3)2 | 90 | 97/3 |
|  | 0.1 | 24 | ZnBr | 86 | 85/15 |
| | | | In(C≡CSiMe3)2 | 80 | 80/20 |
|  | 1.0 | 4 | ZnBr | 93 | 98/2 |
| | | | In(C≡CSiMe3)2 | 93 | 94/6 |
|  | 0.1 | 24 | ZnBr | 90 | 88/12 |
| | | | In(C≡CSiMe3)2 | 80 | 85/14 |
|  | 1.0 | 4 | ZnBr | 89 | 2/98 |
| | | | In(C≡CSiMe3)2 | 88 | 8/92 |
|  | 0.1 | 24 | ZnBr | 89 | 28/72 |
| | | | In(C≡CSiMe3)2 | 80 | 33/64 |

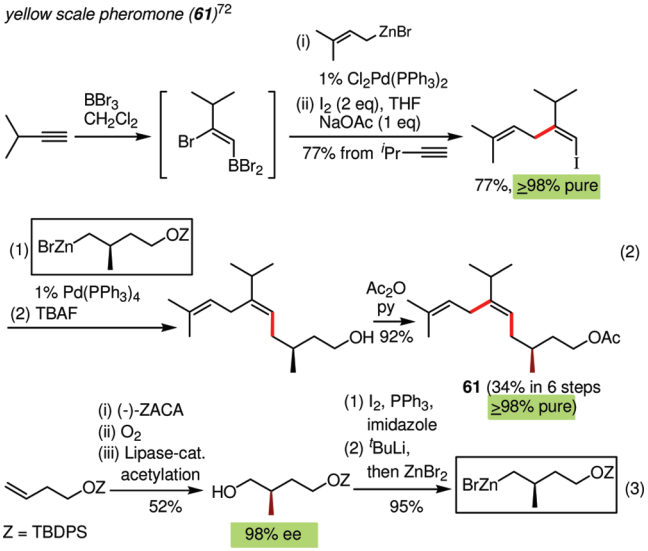
[a]1.2 molar equiv of $Me_3SiC{\equiv}CZnBr$ or 0.4 molar equiv of $(Me_3SiC{\equiv}C)_3In$ was used. [b]Yield by GLC.

Pd-catalyzed enolate substitution.[182] Ideally, it is highly desirable (i) to be able to introduce not only alkyl groups, which is achievable by conventional enolate alkylation, but also various other carbon groups including unsaturated aryl, alkenyl, and alkynyl groups, while (ii) avoiding undesirable double and multiple substitution with (iii) strict control of the site of substitution (α vs α′) and (iv) absolute configuration. Although no full-fledged discussion is intended here, primarily because of its as yet juvenile status, a brief

**SCHEME 40**




*yellow scale pheromone (**61**)*[72]




progress report is presented in the hope of inducing further investigations.

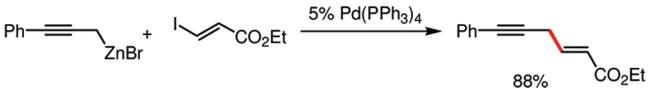
By the mid-1980s, the senior author of this article was convinced that Pd-catalyzed cross-coupling would provide solutions to most, if not all, of the difficulties mentioned above in the y(es)[2] manner according to the master blueprint shown in eq 1, Scheme 44. At first sight, this protocol requiring minimally two steps to **65** and three steps to **66** might appear rather roundabout. In view of (a) the frequently employed regioselective "conjugate reduction" route to regiodefined enolates and more importantly (b) the desirability of developing a satisfactory general route to **65** containing aryl, alkenyl, alkynyl, and other groups as $R^1$, this protocol would be readily justified.

Following the initial proof of concept reported in 1987[183] (eq 2, Scheme 44), a more direct Pd-catalyzed

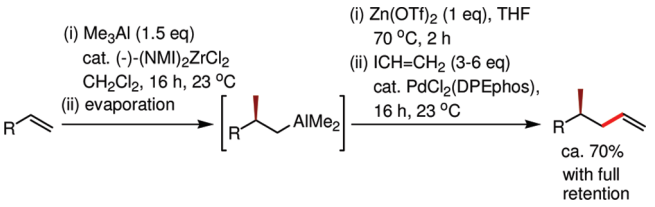
alkenyl−alkenyl coupling route was developed in 1991[184] (eq 3, Scheme 44).

Although asymmetric conjugate reduction of **65** to produce **66** still remains largely undeveloped, recent discoveries of a number of natural products represented by **65** containing alkenyl and alkynyl groups as $R^1$ rendered **65** themselves as new synthetic targets, and their syntheses according to the protocol shown in eq 1, Scheme 44 have been explored and developed significantly by the authors' group[183−187] and those of others, notably Johnson,[188,190] as briefly shown in Scheme 45. In some cases, it was desirable to reduce α-haloenones to α-haloenol derivatives to promote Pd-catalyzed alkenylation. In view of many subsequent developments of Pd-catalyzed alkenylation, however, this additional maneuver may no longer be necessary. In some of these examples, not only trisubstituted but even tetrasubstituted, albeit cyclic, alkenes (types IX and X) are successfully used (Scheme 45).

**SCHEME 41**

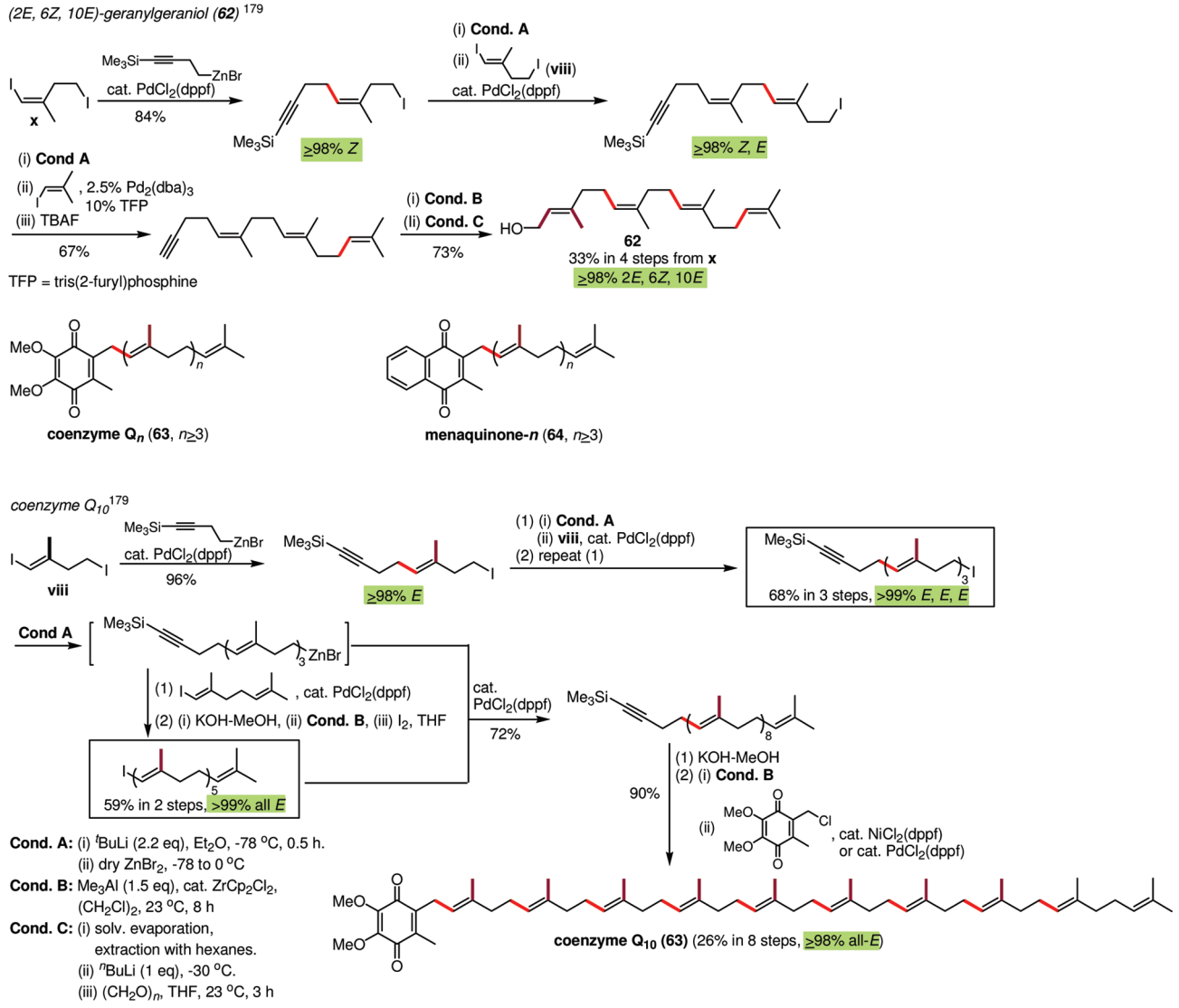



**SCHEME 42**

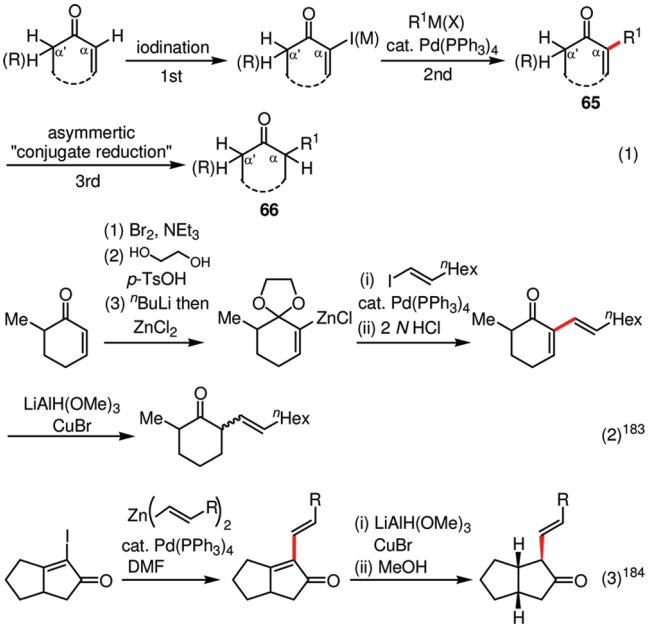



(**6**) **Alkenes via Type IX and X Alkenyl Reagents.** In the preceding section, a few conjugated dienes and trienes containing cyclic tetrasubstituted alkenyl derivatives are shown. Nakienone A, for example, is a conjugated triene preparable via Pd-catalyzed type X alkenyl−type VI alkenyl coupling,[185] while a carbacyclin precursor **68** is accessible via Pd-catalyzed Type IX alkenyl−Type III alkenyl coupling[187] (Scheme 45). It is reassuring that the Pd-catalyzed alkenylation is readily applicable even to such seemingly demanding cases in the

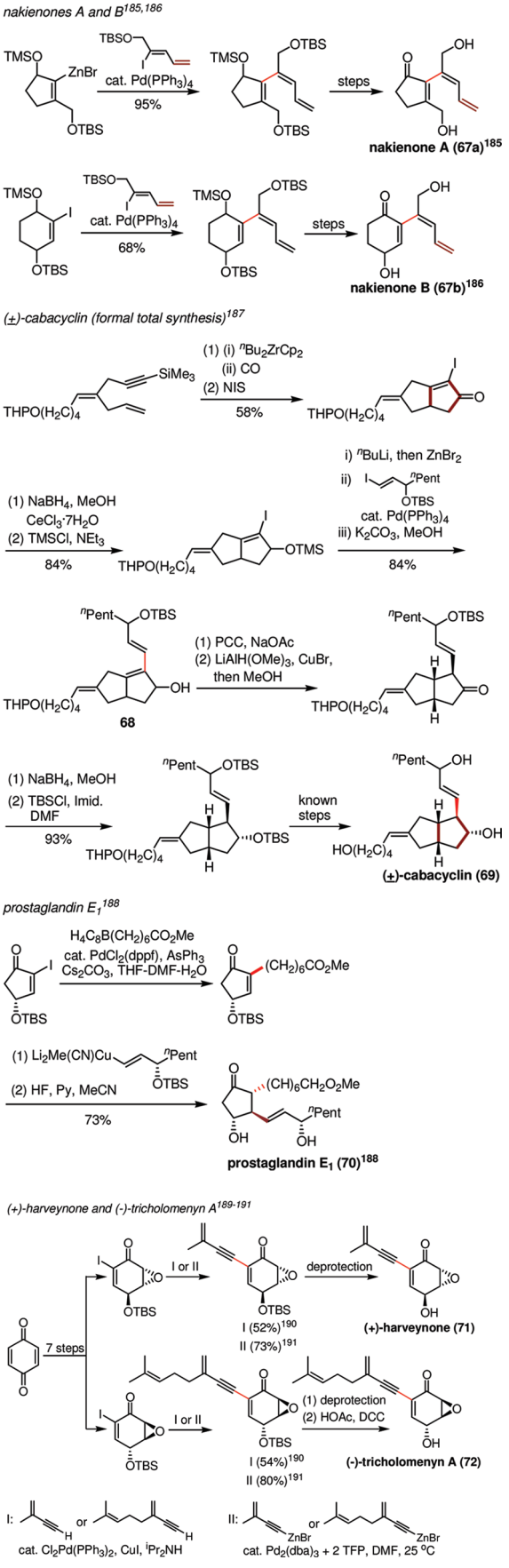
**SCHEME 43**



**SCHEME 44**




**SCHEME 45**

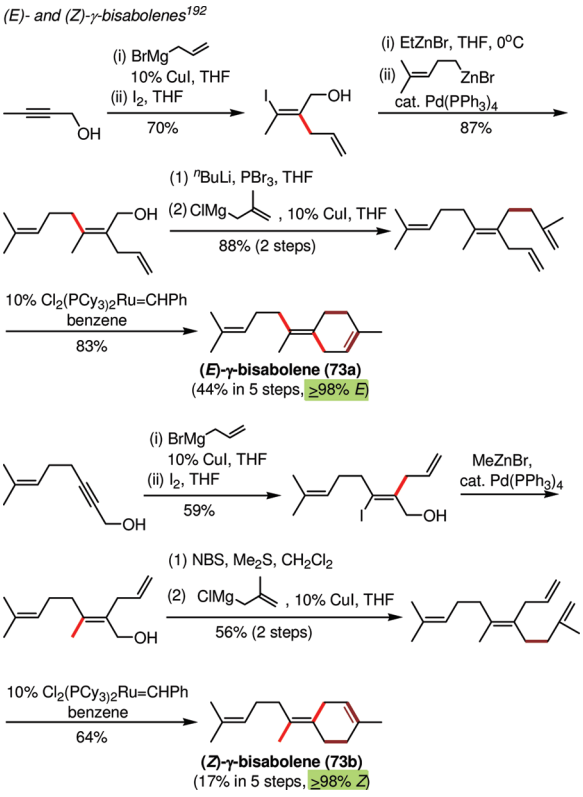



y(es)[2] manner. However, the two examples cited above involve cyclic tetrasubstituted alkenes, the syntheses of which cannot yet be readily discussed in a highly rational and systematic manner. On the other hand, acyclic tetrasubstituted alkenes may be discussed in a more rational and systematic manner. At present, however, the number of such alkenes of natural origin and of biological−medicinal significance is still comparatively small, and the methodology for their syntheses is still very juvenile. From the alkyne elementometalation−Pd-catalyzed alkenylation perspective, any hydrometalation is no longer applicable to their syntheses. Nor is any terminal alkyne usable for this purpose. Thus, carbometalation, "heterometalation", such as halometalation, and metallometalation of internal alkynes displaying high (≥98%) stereoselectivity and practically attractive levels (≥95%) of regioselectivity must be explored and developed.

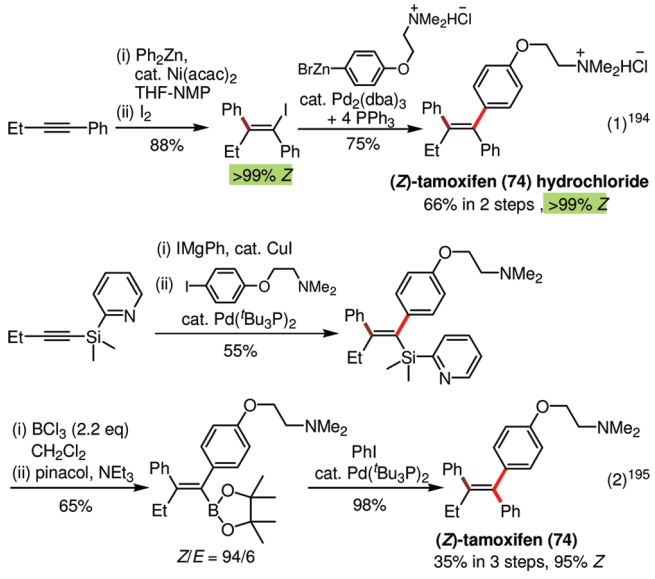
Duboudin Cu-catalyzed *anti*-carbomagnesiation of propargyl alcohol derivatives is one of still a small number of currently known carbometalation reactions of very high (≥98%) regio- and stereoselectivity[88] (eq 3, Scheme 14), which can be profitably exploited, as exemplified by the efficient and highly selective synthesis of both (*E*)- and (*Z*)-γ-bisabolenes (Scheme 46).[192]

It does appear reasonably certain that, as long as the requisite type IX and X alkenyl reagents can be obtained in the y(es)[2] manner, Pd-catalyzed alkenylation, especially the Negishi version, will provide a wide range of tetrasubstituted alkenes of defined regio- and stereochemistry. Even though there still is some room for improvement, evolutionary development of Suzuki alkenylation through rational optimization of several changeable parameters including (a) borane and borate ligands ($BY_2$ and $BY_3M$),[103] (b) Pd catalysts,[193] (c) added promoters, (d) solvent compositions, and others has been continuously improving the mysteriously multitalented boron-based protocol.[72−79] As representative examples of recent developments of tetrasubstituted alkene syntheses in the y(es)[2] manner, the following two routes to an anticancer agent (*Z*)-tamoxifen, one via Ni-catalyzed carbozincation−Negishi coupling[194] and the other via Cu-catalyzed carbomagnesiation−Suzuki coupling[195] are shown in Scheme 47.

**SCHEME 46**




**SCHEME 47**




## Conclusion

In this paper, the current overview of the alkyne (and alkene) elementometalation−Pd-catalyzed cross-coupling routes to alkenes and alkynes is presented. Admittedly, discussions presented herein are biased toward studies conceived and conducted by the authors' group, in part, in the interest of not making this article much longer. A nearly forty-year-long pursuit of discovering, developing, and applying the transition metal-catalyzed cross-coupling as a "LEGO-game" approach to organic synthesis based on the following has led to its current status discussed herein: (1) recognition of "super-carbenoidal" reactivity of *d*-block transition metals in synergistic bond formation and cleavage in readily reversible and catalytic manners, which culminated in the selection of Pd as the optimal catalyst component, (2) screening more than a dozen metals to be used stoichiometrically and judicious selection, of several satisfactory ones including Zn, Al, Zr, B, Cu, and In as well as Mg, (3) discoveries and developments of an ever-expanding assortment of highly satisfactory synthetic routes to the requisite $R^1M$ and $R^2X$ including a wide range of alkyne (and alkene) elementometalation reactions, and (4) increasingly vigorous developments of several other critical aspects including ligands, promoters, cocatalysts, other additives, solvents, and so on.

Although our attention in this article is essentially restricted and focused on Pd-catalyzed alkenylation briefly supplemented with related alkynylation, alkylation, and so on, we feel and believe from a broader perspective that the synthetic methodology based on and centered around Pd-catalyzed cross-coupling has begun rivaling the roughly century-old Grignard and related organoalkali metal-based methodology. Much more significant, however, is that these modern and conventional synthetic methods are mutually more complementary than competitive with each other. At present, we still have to accept the current reality that some classes of cross-coupling including (i) direct alkynyl−alkynyl coupling and (ii) cross-coupling between two allyl and/or propargyl groups in fully controlled and highly desirable manners continue to be difficult and challenging. Fortunately, it has been feasible to develop highly satisfactory alternate Pd-catalyzed cross-coupling routes to the same final products in many of these less than satisfactory cases.

By scanning over the current status of Pd-catalyzed cross-coupling in its entirety, one may begin stating that the synthetic community's task for developing the Pd-catalyzed cross-coupling methodology may be roughly halfway complete. Even so, at least a few more decades of intensive developmental investigations appear to be necessary so as to be able to satisfactorily handle most, if not all, of the fundamentally feasible classes of cross-coupling reactions.

Another important feature that has emerged is the anchoring role of Pd-catalyzed cross-coupling in organic synthesis. Thus, any new and satisfactory methods discovered and/or developed for the preparation of $R^1M$ and $R^2X$ will automatically and continuously keep expanding the synthetic horizon of Pd-catalyzed cross-coupling.

Finally, the basic concept of C−C coupling may be adapted to the discovery and development of any X−Y coupling. Historically, transition-metal-catalyzed C−H coupling, namely catalytic hydrogenation, came first and recognized with the first Nobel Prize for organometallic investigations awarded in 1912 to Paul Sabatier, who shared it with Victor Grignard. Looking into the future, expansion and extension of the more than a century-old C−H coupling and the roughly 40-year-old C−C cross-coupling so as to embrace many other X−Y coupling reactions will prove to be a fruitful area for investigation. In fact, steps in this direction have already been taken with recent works on C−N and C−O coupling reactions, notably by Buchwald[196] and Hartwig,[197] and their further growth and increasing significance may safely be predicted.

**Acknowledgment.** E.N. thanks each of his collaborators whose names appear in the references cited herein and whose invaluable contributions have made the nearly forty-year-long explorations described herein most exciting and fruitful. E.N. also thanks his mentor, the late Professor H. C. Brown, and one of his senior associates, G. Zweifel, for their enormous influences on his research. Outside the Brown school, numerous pioneering works of E. J. Corey on the use of organotransition metals were particularly inspiring in E.N.'s earlier research. Although E.N. refrains from naming any, numerous stimuli of various forms provided by his contemporaneous and younger colleagues have made profound influences on his research. Most of the research performed by the authors's group has been supported by the National Institutes of Health, the National Science Foundation, and Purdue University. E.N. expresses his sincere appreciation of these and other support of his research programs.

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