

BIMETALLIC CATALYTIC SYSTEMS CONTAINING Ti, Zr, Ni, AND Pd. THEIR APPLICATIONS
 TO SELECTIVE ORGANIC SYNTHESSES

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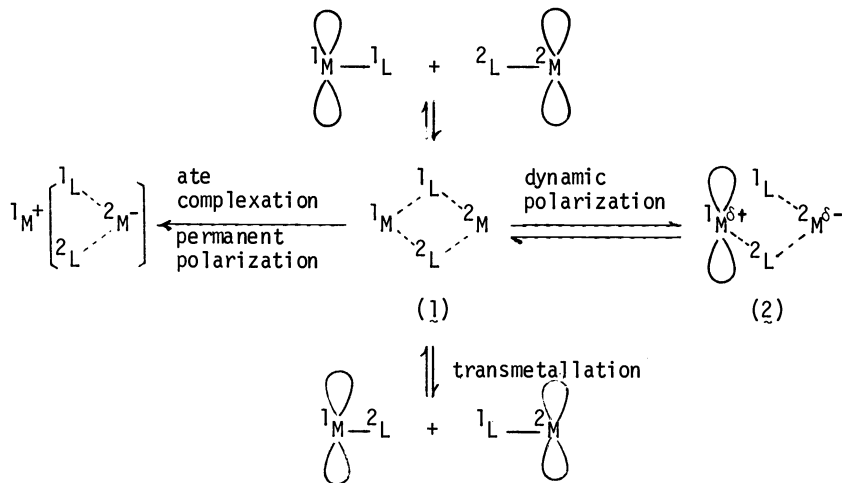
Abstract - Controlled carbometallation of unactivated acetylenes represents a new methodology in organic synthesis. We have found that the Zr-catalyzed carboalumination of terminal alkynes provides a highly selective and versatile entry into trisubstituted olefins, especially those of terpenoid origin. Its scope, synthetic applications, and mechanism are discussed with emphasis on the cross-coupling reactions of alkenylalanes with organic halides catalyzed by palladium and nickel complexes.

INTRODUCTION

Although a number of metallic elements have been shown to be synthetically useful (1), it has become increasingly clear that the synthetic capability of each metal is limited. One potentially promising way of overcoming this limitation would be to consider the simultaneous use of two or more metals. This, in fact, is not a new concept. It will suffice at this point to remind us that the Ziegler-Natta polymerization (2) and the reactions of lithium organocuprates (3) involve bimetallic systems which display reaction characteristics not shared by either of their parent compounds. If all bimetallic combinations were capable of exhibiting certain unique synthetic properties, seventy or eighty metallic elements could provide several thousand additional systems, i.e., bimetallic combinations, for our consideration and use in organic synthesis. This concept can, of course, be extended so as to include multimetallic systems as well. Clearly, what awaits our exploration is far greater than what has already been explored.

Aside from a simple arithmetic argument presented above, is there any scientific or chemical justification for investigating bimetallic systems? Almost by definition, metals can provide metal-carbon bonds in which the metal-bound carbons act as carbanion centers. Until recently, synthetic chemists considered this to be the single-most important property of metals with respect to organic synthesis. More recently, however, the ability of metals to readily provide low-lying empty orbitals has been recognized as a property which is at least as important as the polarized metal-carbon bonds. Coordinatively unsaturated metal-containing species and those capable of readily generating such species have a strong tendency to form bridged dimers and polymers through three-center two-electron bonding. In cases where the participating metals are all identical, such an association process is of little or no synthetic consequence. When two or more metals are different, however, it can lead to various synthetically attractive phenomena. Three such phenomena are shown in Scheme 1.

Scheme 1



In cases where the electronegativity values for $1M$ and $2M$ are substantially different, the more electronegative of the two will attract both of the bridging ligands, i.e., $1L$ and $2L$, inducing ate complexation. Ate complexation can either boost the nucleophilicity of the $2M-2L$ moiety, as in the conversion of organocoppers or organolithiums into $LiCuR_2$ or tone it down, as in the conversion of organolithiums into the corresponding organoborates and organoaluminates (4), (The nucleophilicity of the B-C or Al-C bond is, of course, increased by this process). It can also suppress the often undesirable electrophilicity of the $2M$ center, such as the B and Al atoms of organoboranes and organoalanes, respectively.

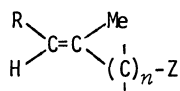
Alternatively, the bridged species 1 may dissociate into two new coordinatively unsaturated species *via* transmetalation. This, in fact, is a ubiquitous process representing one of the most general methods for preparing organometallic compounds. In this review, however, we are primarily concerned with those transmetalation processes that are steps in catalytic cycles involving transition metals. Such catalytic processes make use of the synthetic capabilities of two metals in tandem in one reaction. The Pd-catalyzed cross coupling (5) discussed later, we believe, involves such a process.

Yet another process, which 1 can undergo, may loosely be termed dynamic polarization. Through three-center two-electron bridging, two metal centers can be polarized as shown in 2 . The $1M$ center in 2 is not only coordinatively unsaturated but also positively polarized. Such a metal center must be more electrophilic than that in the original monomer. This mode of activation of a carbon center ($1M = C$) is found in the Friedel-Crafts reaction. What is proposed here is to apply the same principle to activating metal centers in the hope of discovering and developing new synthetic reactions. This review primarily deals with the Zr-catalyzed carboalumination in which activation of one metal by another through dynamic polarization is thought to be of crucial significance.

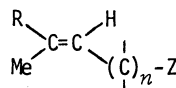
DISCOVERY OF THE ZIRCONIUM-CATALYZED CARBOALUMINATION OF ACETYLENES

Need for selective and versatile routes to trisubstituted olefins

Trisubstituted olefins are present in a wide variety of natural products, especially those of terpenoid origin (6). A large number of such compounds can be represented by either 3 or 4 containing one methyl and two additional carbon groups, at least one of which is often proximally heterofunctional.



(3)

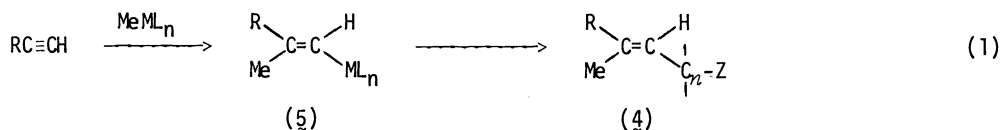
 $n = 1, 2, \text{ etc.}$ 

(4)

Mainly over the past few decades, various methods have been developed for their synthesis (7). The Wittig and related carbonyl olefination reactions are probably the most widely used methods and appear to be reasonably selective and satisfactory for preparing 3 . On the other hand, their use in the selective synthesis of 4 , which would require clean differentiation of the methyl and the R group of the starting ketone, normally leads to the formation of stereoisomeric mixtures. In principle, 3 and 4 are interconvertible, but such interconversions are often cumbersome. Other more stereoselective methods are also known (7), but the stereoselectivity tends to be dependent on substituents and other reaction parameters. Another frequently encountered problem is the lack of versatility. Most of the known methods permit introduction of one or two types of heterofunctional groups (7) (8). When other types of heterofunctionalities are desired, additional steps must be introduced to the synthetic scheme. In light of these difficulties and limitations, we hoped to discover and develop a method for the synthesis of 4 that is (a) stereoselective ($\geq 98\%$), (b) regioselective ($> 95\%$), (c) chemoselective, (d) efficient and convenient, and (e) general with respect to the R and heterofunctional group (Z).

Carbometallation

One conceptually attractive approach would be to achieve addition of a methyl-metal bond to a terminal acetylene, as shown in eq1, and convert the addition product 5 into various types of olefins represented by 4 .

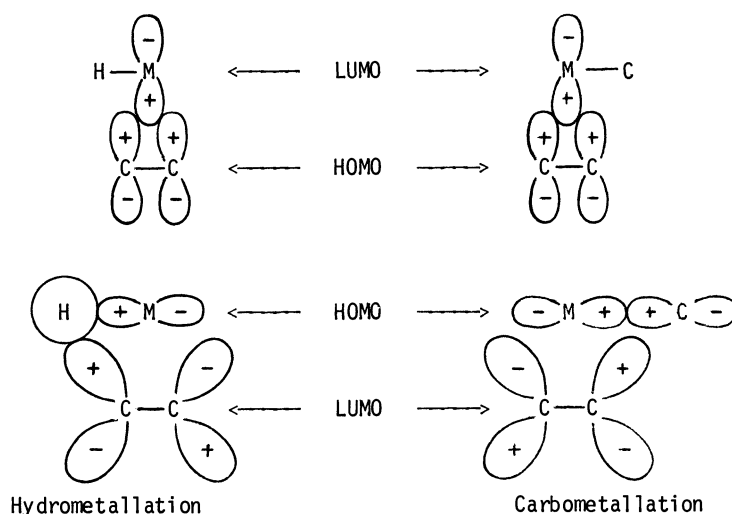


(5)

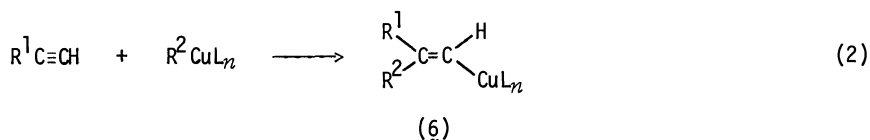
(4)

In principle, those metals that can participate in *cis* hydrometallation can also undergo *cis* carbometallation, although the latter process may be more susceptible to steric hindrance (Scheme 2).

Scheme 2



On the other hand, there is a potential difficulty which is unique to carbometallation. In hydrometallation, the starting compounds, i.e., metal hydrides, and the products are distinctly different. In carbometallation, however, both are organometallic derivatives. Thus, unless their reactivities are significantly different, the products may compete with the reagents for olefins and acetylenes to form polymers. Indeed, our literature survey indicates that, while various metal-containing compounds can undergo carbometallation, carbocupration discovered in 1971 by Normant (9) is essentially the only carbometallation that converts terminal acetylenes into alkenylmetals represented by **6** as discrete products in a highly stereo- and regioselective manner (eq 2).



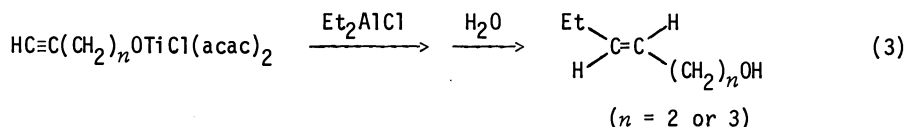
While the significance of the Normant carbocupration as the first synthetically useful controlled carbometallation of terminal acetylenes is undisputable, a few difficulties have also been noted. In the uniquely significant case of addition of the methyl-copper bond, the reaction either fails or becomes exceedingly sluggish. Although a few improved procedures (10) have recently been developed, the above problem does not appear to have been totally solved. In general, alkenylcoppers are relatively unstable above ca. -25°C , which can cause various difficulties in their reactions with electrophiles. Yet another difficulty associated with carbocupration is the capricious nature of the reaction with respect to its regiochemistry observed with acetylenes containing proximal donor groups (9). Clearly, it is desirable to develop additional carbometallation reactions that can complement the synthetic capability of the carbocupration.

Titanium-promoted carbometallation

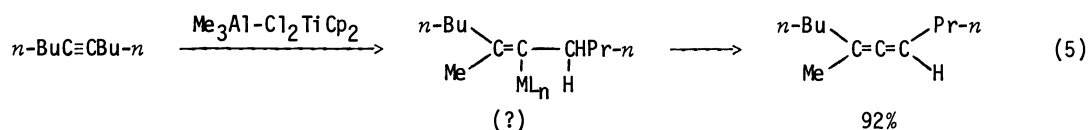
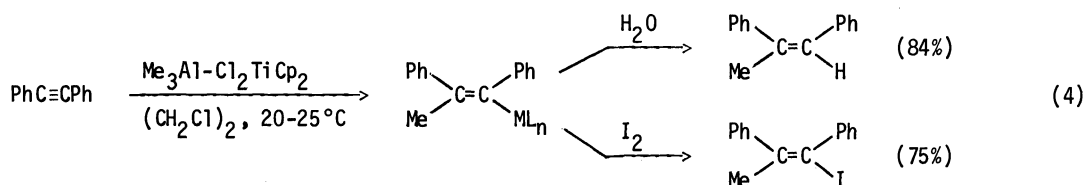
In search for novel and synthetically useful controlled carbometallation reactions of terminal acetylenes, a process of elimination based on considerations of fundamental atomic and bond properties provides a powerful tool. For example, alkali and alkaline earth metals may be ruled out, since organometallics containing such metals would readily abstract the acetylenic proton. The Group IV main group metals, such as Si, Ge, and Sn, may not readily participate in carbometallation unless paired with suitable coordinatively unsaturated metal compounds. Thus, among the main group metals, only the Group IIIA metals, such as B and Al, appear to be potentially capable of undergoing carbometallation. In sharp contrast with boron hydrides (11), however, typical organoboranes appear to be quite inert to acetylenes (12), which may be attributable to the fact that organoboranes are highly sensitive to steric hindrance. On the other hand, organoalanes are known to undergo carboalumination with acetylenes at elevated temperatures (13). Under such conditions, however, terminal acetylenes suffer from extensive abstraction of the acetylenic proton. It then occurred to us that Al-Ti reagent systems used in the Ziegler-Natta olefin polymerization (2) should, in principle, be capable of carbometallating acetylenes. An intriguing question is how to exploit or modify reagent systems which induce a series of carbometallation reactions of olefins so as to achieve a single-stage addition to acetylenes.

It was reported in 1976 that titanium complexes derived from alkynols and $\text{Cl}_2\text{Ti}(\text{acac})_2$ reacted with Et_2AlCl to give, after hydrolysis, the corresponding ethylated alkynols (14).

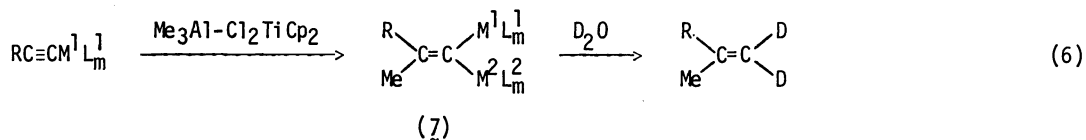
Unfortunately, the reaction was only of very limited scope, requiring alkynols of appropriate chain length ($n = 2$ or 3) (eq 3).



Although the above-described results were not very encouraging, we undertook to examine the reaction of acetylenes with one of the simplest and homogeneous Al-Ti reagent systems, i.e., $\text{Me}_3\text{Al}-\text{Cl}_2\text{TiCp}_2$ ($\text{Cp} = \eta^5\text{-C}_5\text{H}_5$). We have indeed found that the reagent system reacts smoothly with diphenylacetylene to give a product which produces (*Z*)-1,2-diphenylpropene in 84% yield on hydrolysis and (*E*)-1-iodo-1,2-diphenylpropene in 75% yield on iodolysis (15) (eq 4). As such, this reaction too is of very limited scope. Thus, alkyl-substituted internal acetylenes, such as 5-decyne, directly gives allenes instead of olefins (eq 5), and the yields of the carbometalated products obtained from terminal acetylenes are very low ($\leq 30\%$), the unidentified major products being oligomeric (15).

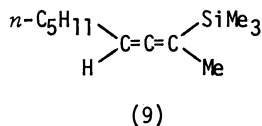
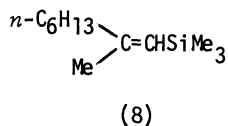


To circumvent the undesirable oligomerization, we prepared terminally metal-substituted acetylenes containing ZnCl , BR_2 , AlR_2 and SiR_3 and examined their reaction with $\text{Me}_3\text{Al}-\text{Cl}_2\text{TiCp}_2$. We were pleased to find that all of the above metal-substituted acetylenes reacted smoothly with the Al-Ti reagent system. In the cases of Zn, B and Al containing acetylenes, deuterolysis of the carbometallation products gave 1,1-dideuterio-2-methylalkenes in 75-85% yields, indicating that these reactions took place according to eq 6 (15).

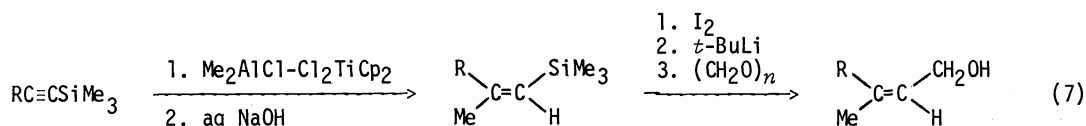


$\text{M}^1\text{L}_m^1 = \text{ZnCl}, \text{BR}_2 \text{ or } \text{AlR}_2$. $\text{M}^2\text{L}_m^2 = \text{Al- and/or Ti-containing group}$.

Although the carbometallation products 7 could serve as useful intermediates for tri- and tetrasubstituted olefins, we have not yet succeeded in cleanly differentiating the two metal-containing groups. The reaction of 1-octynyltrimethylsilanes with $\text{Me}_3\text{Al}-\text{Cl}_2\text{TiCp}_2$ produced a 70:30 mixture of 2-methyl-1-trimethylsilyl-1-octene (8) and 2-trimethylsilyl-2,3-nonadiene (9) in 80% combined yield (15).



Shortly after we published the above results, a few other related studies describing similar but somewhat different results have appeared. Eisch has reported that treatment of alkynylsilanes with $\text{RAlCl}_2-\text{Cl}_2\text{TiCp}_2$ or $\text{R}_2\text{AlCl}-\text{Cl}_2\text{TiCp}_2$ in CH_2Cl_2 followed by addition of Et_3N and then water results in stereoisomeric mixtures in which the products of *trans* addition often predominate (16). A subsequent study by Snider (17) has established that the reaction of alkynylsilanes with $\text{Me}_2\text{AlCl}-\text{Cl}_2\text{TiCp}_2$, but not $\text{Me}_3\text{Al}-\text{Cl}_2\text{TiCp}_2$, produces neither allenes nor significant amounts of *trans* addition products. Treatment of the carbometallation products with aqueous NaOH gives $\sim 95\%$ pure (*Z*)-alkenylsilanes in good yields, which can be converted into (*Z*)-trisubstituted olefins by known procedures (eq 7). The overall operation, however, is rather cumbersome.



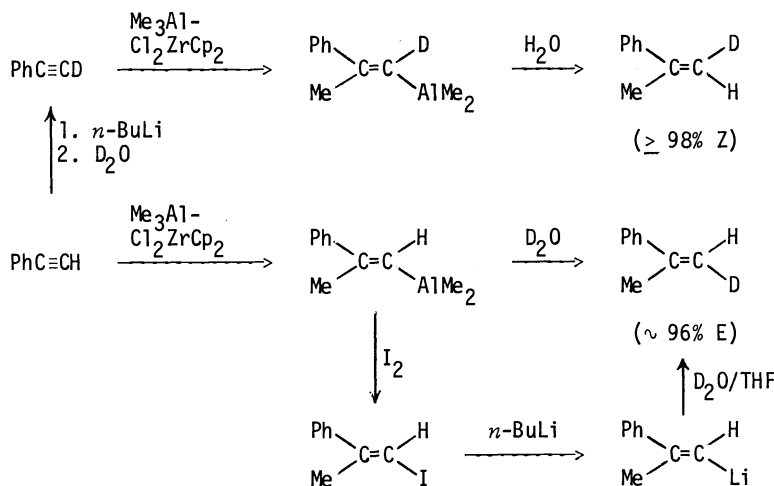
In summary, although the carbometallation of alkynylsilanes with Al-Ti reagent systems is promising, a highly satisfactory route to trisubstituted olefins based on the reaction is yet to be developed.

Zirconium-catalyzed carboalumination

The difficulties encountered in our study with Al-Ti reagent systems led us to suspect that the Al-Ti combination might not be best suited for carbometallation of acetylenes. Rather than modify the structural features of reagents and/or substrates and vary other reaction parameters, we decided to search a better-suited metal to be used in conjunction with Al. We felt that one of the most logical approaches to be taken in a situation like this would be to consider all three transition metals of a triad of interest. Accordingly, we began investigating the Al-Zr and Al-Hf combinations. It was also known to us that certain Al-Zr reagents systems can induce the Ziegler-Natta-type olefin polymerization, although their reactivity is considerably lower than that of the corresponding Al-Ti systems (18). We felt that the lower reactivity of the Al-Zr systems just might be well suited for achieving a single-stage carbometallation.

Our first experiment with $\text{Me}_3\text{Al}-\text{Cl}_2\text{ZrCp}_2$ turned out to be a major success. Thus, addition of Me_3Al to Cl_2ZrCp_2 suspended in 1,2-dichloroethane produced a lemon yellow homogeneous solution. Addition of phenylacetylene, induced a smooth carbometallation at room temperature, producing an intermediate which, on protonolysis, gave a 95:5 mixture of α -methylstyrene and propenylbenzene in 100% combined yield (Scheme 3) (19).

Scheme 3

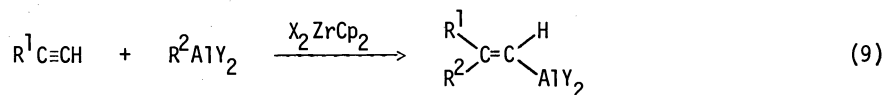
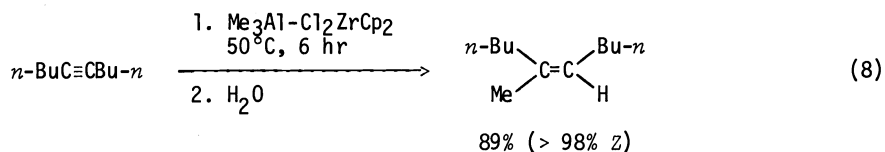


Deuterolysis of the intermediate gives (*E*)- β -deuterio- α -methylstyrene of 96% stereoisomeric purity, indicating that an alkenylmetal species is formed as a discrete intermediate. The actual stereoselectivity of the reaction is $\geq 98\%$, as indicated by the results obtained with deuteriophenylacetylene (Scheme 3). Iodolysis of the intermediate gives (*E*)- β -iodo- α -methylstyrene in 73% yield, the stereochemistry of which has been established by lithiation-deuterolysis (Scheme 3). The ^1H NMR spectrum of the reaction mixture indicates that essentially 100% of Cl_2ZrCp_2 remains unchanged, as judged by the integration of the Cp singlet at δ 6.45 ppm. No other signal corresponding to the Cp group is discernible in the expected region, indicating that the carbometallation product, which exhibits an allylic proton signal at δ 2.35 ppm, must be (*E*)-(2-phenylpropenyl)dimethylalane. The results also indicate that the reaction must be catalytic in Cl_2ZrCp_2 . Indeed, the reaction proceeds to $> 90\%$ completion within one day even with 5-10 mol % of Cl_2ZrCp_2 .

We have also found that the reaction of phenylacetylene with $\text{Me}_3\text{Al}-\text{Cl}_2\text{HfCp}_2$ proceeds in a manner similar to that observed with Cl_2ZrCp_2 (19). Although Cl_2HfCp_2 we used contained $\sim 5\%$ of Cl_2ZrCp_2 , the reaction was far faster than when only 5 mol % of Cl_2ZrCp_2 was used. We therefore conclude that we indeed observed a reaction of an Al-Hf system. However, we have not yet observed any feature of the Al-Hf reaction which is significantly different from that of the Al-Zr reaction. At this stage of our study, we felt that we might have finally found one highly satisfactory bimetallic system for carbometallation of acetylenes in the Al-Zr combination.

SCOPE OF THE ZIRCONIUM-CATALYZED CARBOALUMINATION OF ACETYLENES

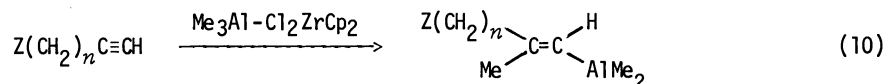
Although internal acetylenes, e.g., 5-decyne, can readily participate in the Zr-catalyzed carboalumination (e.g., eq 8), it would be difficult to achieve a high regioselectivity in the reaction of unsymmetrically substituted internal acetylenes. In exploring the scope of the Zr-catalyzed carboalumination, we have therefore focused our attention on the R¹ and R² groups in eq 9.



Scope with respect to the R¹ group. The zirconium-catalyzed carboalumination of proximally hetero-functional acetylenes

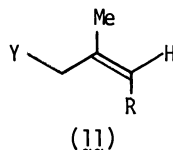
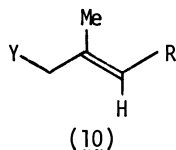
The Zr-catalyzed carboalumination has proved to be highly general with respect to the R¹ group of terminal acetylenes (R¹C≡CH). Various alkyl groups, conjugated alkenyl groups, e.g., vinyl and propenyl, isolated alkenyl groups, e.g., homoallyl, phenyl, and even hydrogen, i.e., acetylene itself, can readily be carbometallated with Me₃Al-Cl₂ZrCp₂ to give, after hydrolysis, the methylated alkenes in 90-100% yields. The regioselectivity observed with these hydrocarbon-substituted acetylenes has been 95-100%.

For the Zr-catalyzed carboalumination to be truly useful in organic synthesis, however, it should be able to accommodate some hetero-functional groups, especially those that are proximal to the acetylene group. In this connection, it is worth noting that all previously reported controlled carbometallation reactions of propargyl and homopropargyl derivatives containing donor-type groups (9) (14) (20) either are nonregio- and/or nonstereoselective or display regioselectivity opposite to that which is observed with simple alkynes, presumably due to marked directive effects of the proximal hetero atoms. In marked contrast with these known reactions, the Zr-catalyzed carboalumination displays a uniformly high regio- and stereoselectivity with propargyl and homopropargyl derivatives containing OH, OSiMe₂Bu-*t*, SPh or iodine groups (eq 10) (21).



Z = OH, OSiMe₂Bu-*t*, SPh, I. n = 1 or 2.

In a few representative cases, the *cis* stereochemistry of the addition has been rigorously established (21). In the other cases, the stereochemical assignments are based on a tentative but seemingly reliable generalization (22) that the ¹³C NMR signals for the allylic methyl carbons of 10 and 11 appear ca. 16±3 and ≥ 19 ppm, respectively.

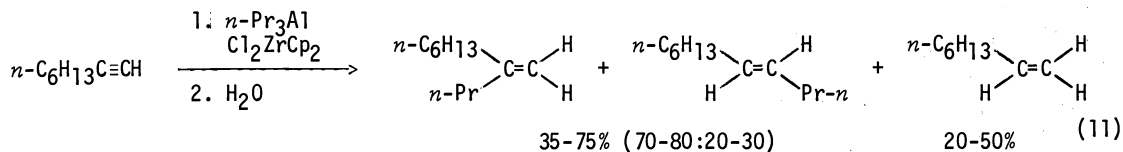


Y = carbon or hetero atom group. R = carbon group.

Although the regioselectivity of these reactions is somewhat dependent on the proximal hetero atoms, it has nonetheless been uniformly high, ranging from 92 to 100%, except for the case of homopropargyl phenyl sulfide which displays a regioselectivity of 86% with Me₃Al-Cl₂ZrCp₂. Fortunately, it can be improved to ≥ 98% by using Me₃Al-Me₂ZrCp₂, although the precise reason for the improvement is unclear. The regioselectivity observed with propargyl derivatives is generally ≥ 98%, which is somewhat higher than that observed with homopropargyl derivatives (mostly 92-94%). It is possible that the undesirable regioisomers in the case of propargyl derivatives decompose *via* β elimination under the reaction conditions, although this point is yet to be clarified. As described later, the Zr-catalyzed carboalumination of proximally hetero-functional acetylenes provides a versatile route to difunctional trisubstituted olefin synthons for the synthesis of a variety of natural products of terpenoid origin.

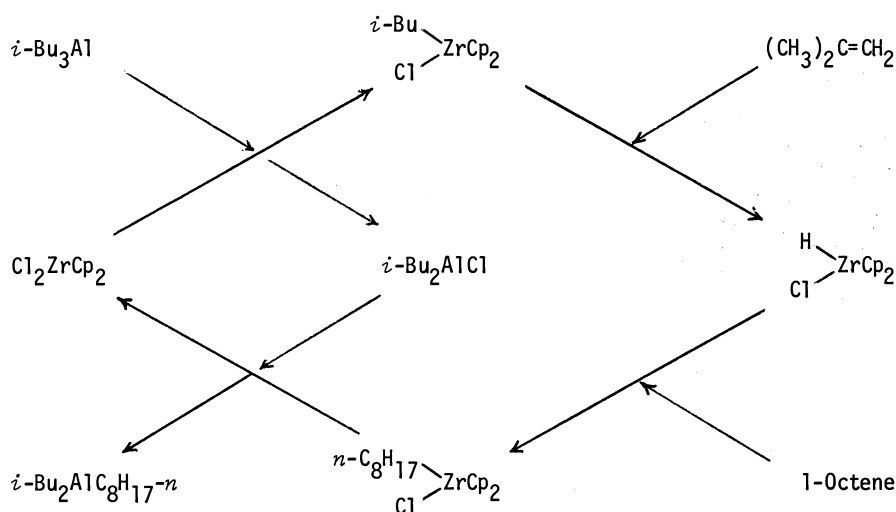
Scope with respect to the R² group. The zirconium-catalyzed hydroalumination of olefins Although addition of the methyl-metal bond across the C=C bond is uniquely important because of its potential usefulness in the selective synthesis of terpenoids and other related natural products, we are also interested in exploring the scope of the Zr-catalyzed carboalumination with respect to the R² group of organoalanes (R²AlY₂).

In the reaction of 1-octyne with *n*-Pr₃Al-Cl₂ZrCp₂, two difficulties were encountered. First, the regioselectivity was only 70-80%. Second, the yield of the carbometallation products decreased to 35-75%. Formation of 1-octene in 20-50% yield on hydrolysis of the reaction mixture indicates that the carbometallation reaction is competed by hydrometallation (eq 11).



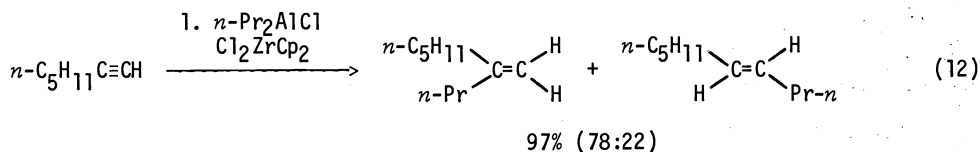
Indeed, when *i*-Bu₃Al or *t*-Bu₃Al was used in place of *n*-Pr₃Al, the reaction proceeded exclusively *via* hydrometallation (23). The hydrometallation reaction of acetylenes under these conditions has not yet been fully developed as a synthetically useful method. On the other hand, the corresponding reaction of monosubstituted olefins proceeds well to give the hydro-metallation products in 85-100% yields (23). Examination of the reaction mixture by ¹H NMR indicates that R(Cl)ZrCp₂ (δ 6.22 ppm for the Cp group) is initially formed, but that the eventual product is an organoalane. In accord with these observations, the reaction has been shown to be catalytic in Cl₂ZrCp₂. These facts can be nicely accommodated by the four-step mechanism for the case of *i*-Bu₃Al shown in Scheme 4. Both the hydrozirconation (24) and conversion of organozirconium species into organoalanes (25) are well documented.

Scheme 4



Although the full scope of this novel Zr-catalyzed hydroalumination remains to be established, it does provide an attractive alternative to the conventional hydroalumination, which is generally incapable of coping with donor-type substituents. Thus, allyl phenyl sulfide, alkenols, e.g., 4-penten-1-ol, and 5-bromo-1-pentene are readily converted into terminally (> 95%) Al-substituted organoalanes in 85-95% yields (23).

We have recently found that the competitive hydrometallation reaction can be readily suppressed, although the regiochemical problem still persists. As discussed later in detail, the *n*-Pr₂AlCl-Cl₂ZrCp₂ system does not undergo a facile *n*-Pr-Cl exchange (26) required for the Zr-catalyzed hydroalumination (Scheme 4). As might be predicted on the basis of the mechanism shown in Scheme 4, its reaction with 1-heptyne gives, after hydrolysis, a 78:22 mixture of 2-*n*-propyl-1-heptene and (*E*)-4-decene in 97% combined yield with no more than a trace, if any, of 1-heptene (eq 12) (26).



The results presented above not only provides a handy solution to the problem arising from the competitive hydrometallation, but have a significant bearing on the mechanism of the Zr-catalyzed carboalumination, as discussed later.

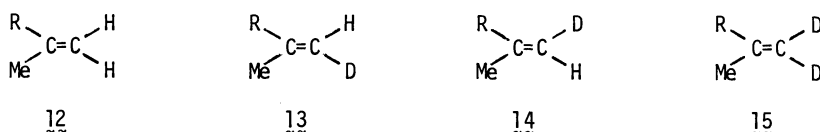
We have not so far made serious attempts at observing addition of carbon-metal bonds containing alkenyl, aryl, alkynyl, and other types of organic groups. It should, however, be noted that the alkenylalanes formed as the carbometallation products do not compete with trialkylalanes for acetylenes, presumably because the alkenyl bridging in alkenylalanes, which is known to be more effective than the alkyl-bridging, deactivates alkenylalanes toward carbometallation relative to alkylalanes. This presents an intriguing dichotomy, since the same enhanced bridging ability of the alkenyl group is thought to be responsible for the greater reactivity of the alkenyl-Al bond, as compared with the alkyl-Al bond, in a wide variety of organoaluminum reactions.

SYNTHETIC APPLICATIONS OF THE ZIRCONIUM-CATALYZED CARBOALUMINATION

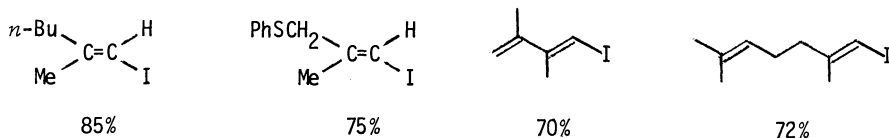
Formation of carbon-hetero atom bonds

When we learned that the carbometallation products are alkenylalanes, we felt that we had just discovered a highly versatile route to trisubstituted olefins, since a large number of synthetically useful reactions of alkenylaluminum compounds had already been developed by us and others, most notably Zweifel and his associates (27).

(a) Protonolysis and deuteration. The alkenyl-aluminum bond is readily hydrolyzed with water. The use of D_2O incorporates deuterium in olefins. These reactions usually proceed quantitatively with complete retention of the olefin geometry (28). As indicated in Scheme 3, geminally disubstituted olefins containing zero, one or two deuterium atoms, especially those that are monomethyl substituted, i.e., 12-15, can now be readily prepared using terminally protonated or deuterated acetylenes.

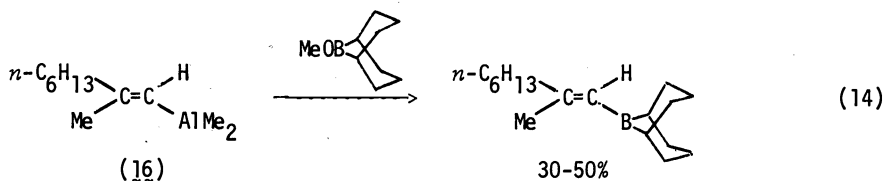
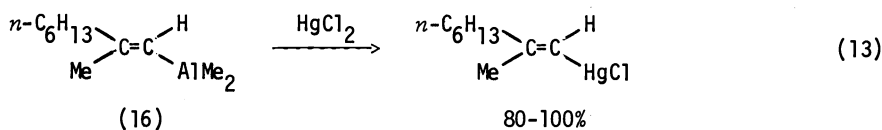


(b) Halogenolysis. It is known that (*E*)- β -monosubstituted alkenylalanes can be converted into the corresponding chlorides, bromides, and iodides by treatment with $NCS(Et_2O, -30^\circ)$, $Br_2(Et_2O\text{-pyridine}, -78^\circ)$, and $I_2(THF, -78^\circ)$, respectively (29). Although we have not yet tried chlorinolysis or brominolysis of the carbometallation products, their iodinolysis indeed proceeds cleanly to give the corresponding alkenyl iodides, that are $\geq 98\%$ *E*, in 70-85% yields (30).



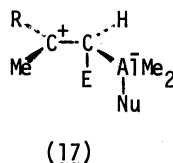
Although 1 equivalent of an alkenyldimethylalane can consume 3 equivalents of iodine, the use of 1.2 equivalents of iodine is normally sufficient, indicating that the alkenyl-Al bond is considerably more reactive than the Me-Al bond. Furthermore, the regioisomeric purity of the alkenyl iodide products obtained under these conditions are often $\geq 98\%$, indicating that the regioisomeric alkenylalane intermediates are considerably less reactive than the major alkenylalanes. Indeed, in this and many other reactions discussed later, the use of a slightly deficient amount of a reagent leads to the formation of the desired product which is regiochemically $\geq 99\%$ pure. Other non-metallic hetero atoms of our interest include O, S, Se, N, and P. The preparation of stereo- and regiodefined enolates and enol ethers appears to be particularly attractive. However, we have not yet made a detailed study of these aspects.

(c) Transmetalation. Since Al is about the only metal that can be readily incorporated in alkenylmetals represented by 5, it is desirable to develop convenient procedures for converting alkenylalanes into various alkenylmetals. Some metals of our interest include Zn, Cd, Hg, B, Si, and Sn. Although a large number of transmetalation reactions of organoalanes are known (28), relatively few involve clean transmetalation. We have just started a systematic study of the transmetalation reactions of alkenylalanes. Some of the preliminary results are highly promising. The reaction of (*E*)-(2-methyl-1-octenyl)dimethylalane (16) with $HgCl_2$ is exothermic and produces (*E*)-2-methyl-1-octenylmercuric chloride in quantitative yield (eq 13) (31). At present, the reaction of 16 with *B*-methoxy-9-borabicyclo[3.3.1]nonane is less clean than the mercuriation shown in eq 13, the yield of *B*-(2-methyl-1-octenyl)-9-borabicyclo[3.3.1]nonane being 30-50% (eq 14) (32). Efforts are being made to improve the results in our laboratories.



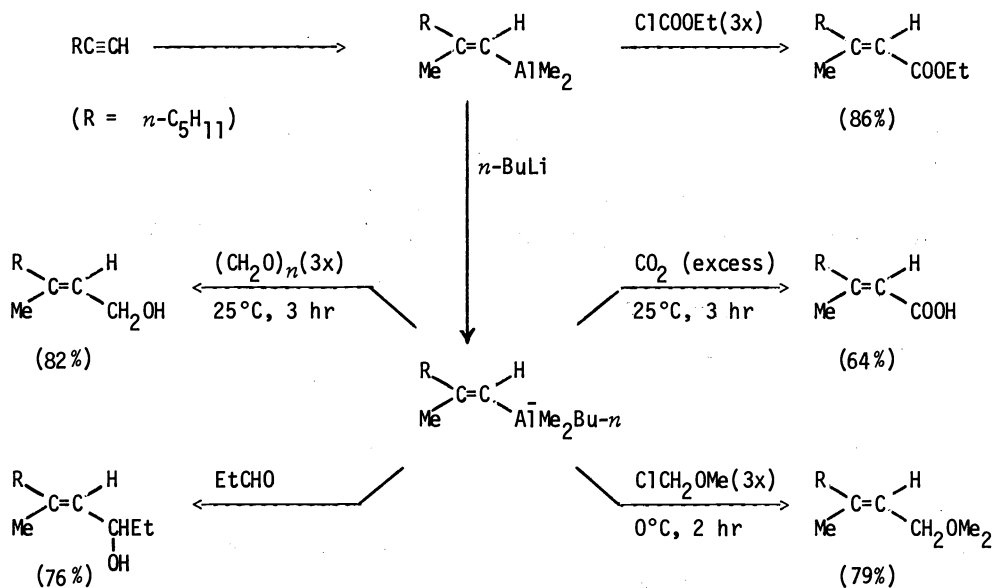
Formation of carbon-carbon bonds *via* uncatalyzed reactions of alkenylaluminums

Prior to our discovery of the Zr-catalyzed carboalumination, several groups of workers including ourselves had developed various carbon-carbon bond-forming reactions of alkenylaluminums (27). As all alkenylaluminums previously employed in these reactions are either β -monosubstituted or α,β -disubstituted, one of our initial concerns was whether the β,β -disubstituted carbometallation products might behave markedly differently, thereby affecting the yield and/or the stereoselectivity. Since one plausible mechanism for their reactions with reagents E-Nu may involve a zwitterionic intermediate 17, in which a carbocationic center develops on the β -carbon, our concern appeared to a legitimate one.

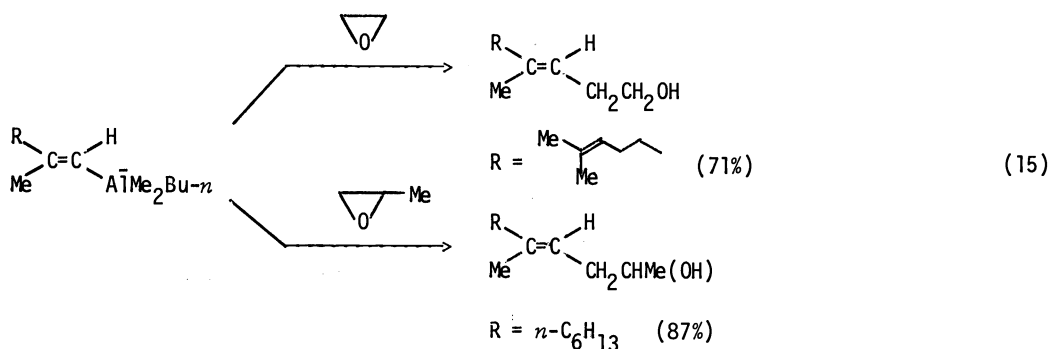


We were therefore pleased to find that both alkenyldimethylalanes and their ate complexes, generated *in situ* by treating them with 1 equivalent of *n*-BuLi after evaporation of the solvent for carbometallation and filtration of Cl_2ZrCp_2 , reacted smoothly with several one-carbon homologation reagents, i.e., ClCOOEt (33), CO_2 (34), $(\text{CH}_2\text{O})_n$ (34), aldehydes (35), and $\text{ClCH}_2\text{OCH}_3$ (36), with essentially complete retention ($\geq 98\%$) of the olefin geometry (Scheme 5), (31)(37).

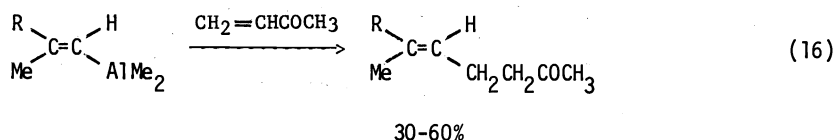
Scheme 5



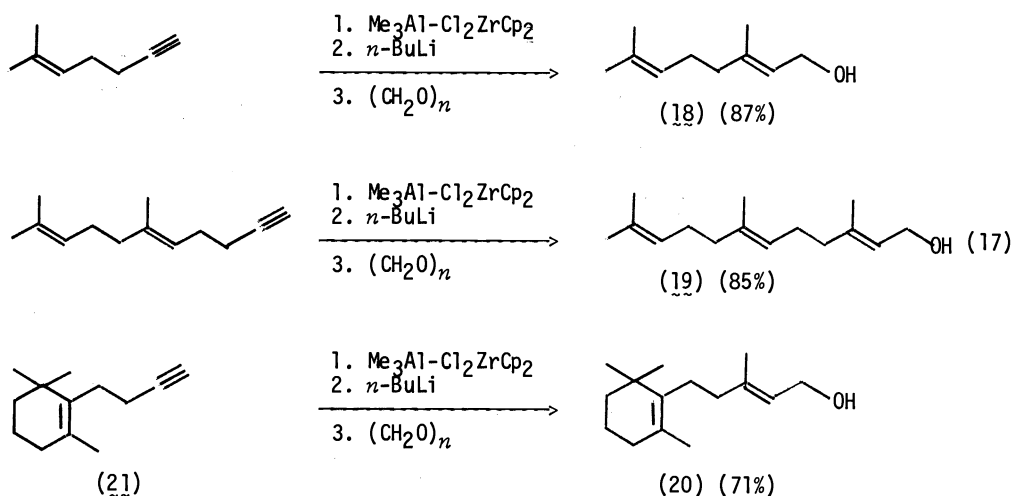
Similarly, the reaction of alkenylaluminates with ethylene oxide and monoalkyl substituted epoxides (38) produced the corresponding hydroxyethyl derivatives in high yields with complete retention of the stereochemistry (eq 15) (39).



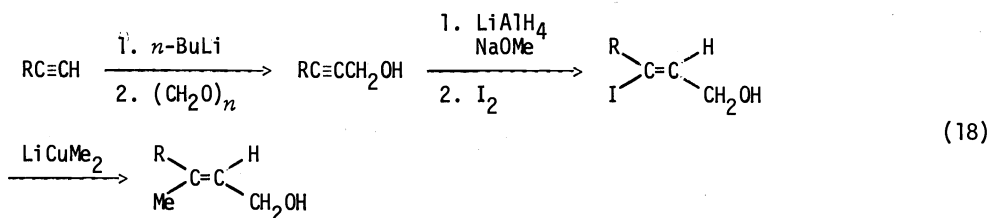
Although a three-carbon homologation reaction of alkenylalanes *via* conjugate addition (40) is known, the yields of the products observed with methyl vinyl ketone have been in the 30-60% range (eq 16) (32). Attempts are being made to overcome this difficulty.



Some of these carbon-carbon bond-forming reactions can now be directly applied to the synthesis of terpenoids, as exemplified by the following syntheses of geraniol (18) (37), farnesol (19) (41), and monocyclofarnesol (20) (42). It should be emphasized that the overall transformation is highly stereo- and regioselective, producing pure products without extensive isomer separations.



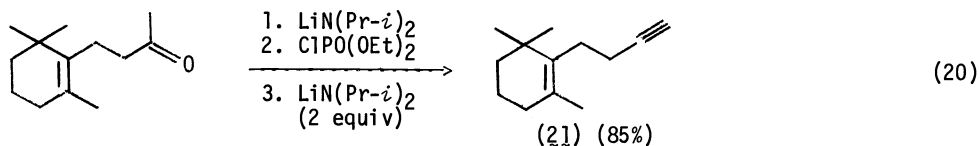
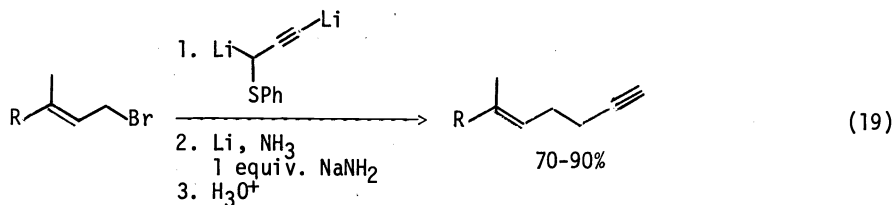
This one-step procedure should be compared with a previously developed three-step procedure shown in eq 18 (43).



The synthesis of the required 1,5-enynes proved to be a nontrivial task. All previously known methods for preparing 1,5-enynes *via* allyl-propargyl coupling (44) are only of marginal synthetic utility due to low product yields. On the other hand, the cross-coupling reaction of 1,3-dilithiopropargyl phenyl sulfide with allylic bromides followed by reduction with Li in liquid NH_3 produces 1,5-enynes in 70-90% yields (eq 19) (45).

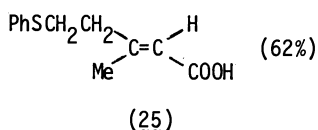
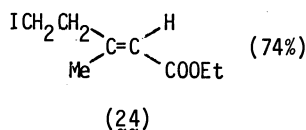
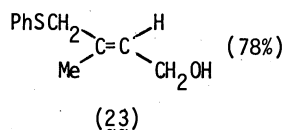
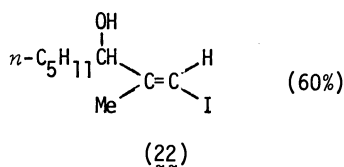
Likewise, various known methods for converting methyl ketones into terminal acetylenes were

rather disappointing. We have therefore developed a one-pot procedure represented by the following conversion of dihydro- β -ionone into **21** (eq 20) (42). Lithium diisopropylamide is highly satisfactory in cases where the R group either does not contain an α -hydrogen atom or is highly hindered (80-85% yields). Otherwise, sterically more hindered amides, such as lithium 2,2,6,6-tetramethylpiperide, are required.



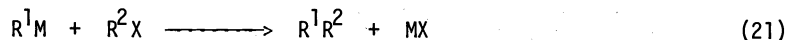
Admittedly, our target molecules are very simple. However, these highly efficient and selective procedures should be directly applicable to the synthesis of more complex terpenoids and related compounds as well.

It should also be pointed out that the Zr-catalyzed carboalumination of proximally hetero-substituted acetylenes followed by displacement of the Al-containing groups with hetero-functional substituents provides an efficient, selective and versatile route to difunctional tri-substituted olefin synthons, such as **22-25** (21).

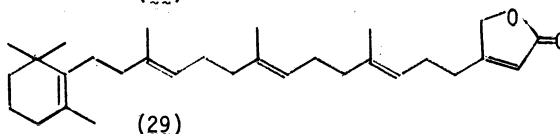
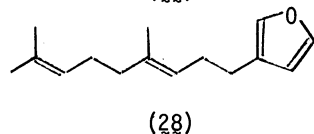
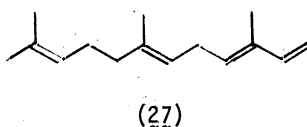
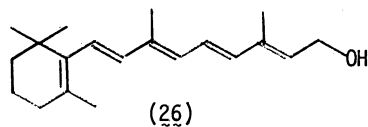


Formation of carbon-carbon bonds *via* the palladium- or nickel-catalyzed cross coupling

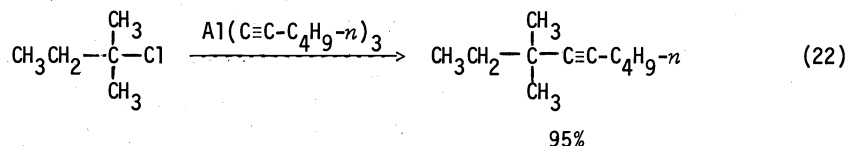
Cross coupling involving the reaction of organometallic species with organic halides and related electrophiles represents one of the most straightforward methods of carbon-carbon bond formation (eq 21).



If the alkenylaluminum derivatives obtained by the Zr-catalyzed carboalumination of acetylenes readily undergo cross coupling, their versatility as intermediates for trisubstituted olefins of terpenoid origin would be vastly enhanced. More specifically, we hoped to develop efficient and selective procedures for (a) conjugated dienes and polyenes, e.g., vitamin A (**26**) (46), (b) 1,4-dienes and related polyenes, e.g., α -farnesene (**27**) (47), and (c) 1,5-dienes and related polyenes, e.g., dendrolasin (**28**) (48) and mokupaide (**29**), (49).

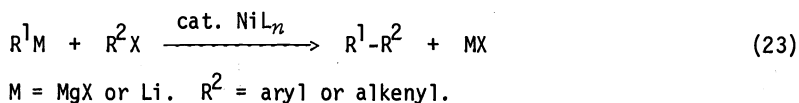


Although organoaluminums are capable of undergoing certain otherwise difficult cross-coupling reactions at electrophilic tertiary carbon centers, as exemplified by the results shown in eq 22 (50), their reactivity as "Grignard-like" nucleophiles is severely limited.



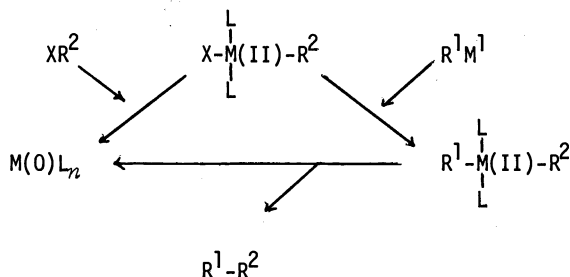
The nucleophilicity of alkenylalanes can be significantly enhanced by converting them into their ate complexes (27). Even so, only some of the most reactive alkyl halides, such as methyl iodide, allyl bromide, and propargyl bromide, give satisfactory results, the results with other typical alkyl halides, such as *n*-octyl iodide, benzyl bromide, and substituted allylic halides, being at best modest (< 50% yields) (51)(52).

After making some unsuccessful attempts to promote the cross-coupling reaction of alkenylaluminums with Cu-containing reagents, we decided to explore the possibility of catalyzing the reaction with transition metal complexes. In 1972, Kumada (53) and Corriu (54) independently reported that the reaction of Grignard reagents or organolithiums with alkenyl and aryl halides could be markedly catalyzed by certain Ni-phosphine complexes (eq 23).



Although this reaction might be considered as a variation of the so-called Kharasch reaction (55), use of metal-phosphine complexes as catalysts had not been explored in detail prior to their studies. While the precise mechanism of the reaction remains to be further clarified, the following scheme consisting of an oxidative addition-transmetalation-reductive elimination sequence proposed by Kumada (53) appears to be plausible in many cases.

Scheme 6



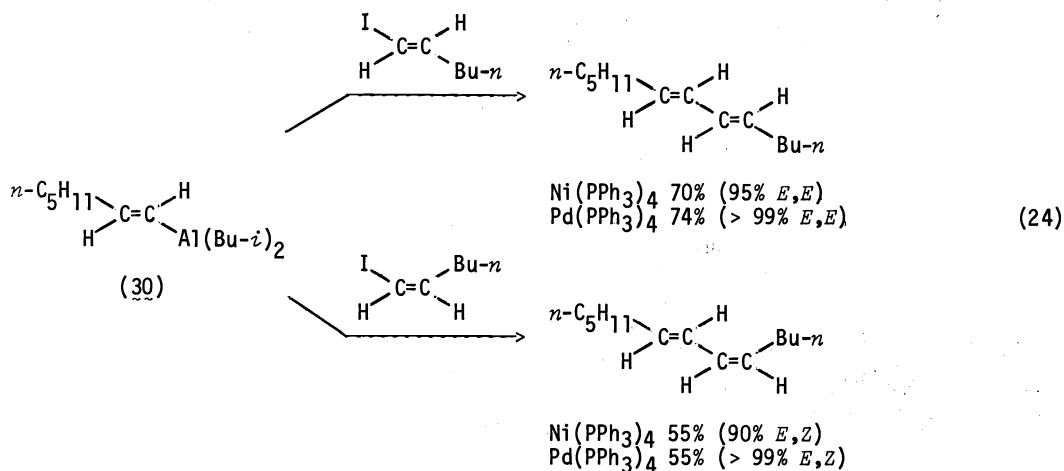
The products of the Ni-catalyzed cross coupling reported in the initial papers by Kumada (53) and Corriu (54) were those which could also be readily prepared by organocopper reactions. Thus, the unique synthetic advantages of this new cross-coupling reaction were virtually unknown. Furthermore, it was evident that the use of organolithiums and Grignard reagents would severely limit the range of functionalities that could be tolerated in the reaction. Nonetheless, we were strongly attracted by the possibility that Scheme 6 might represent a general and useful approach to selective carbon-carbon bond formation *via* cross coupling, the scope of which might possibly be far wider than indicated by the known results. Some of the specific questions to which we addressed ourselves were the following:

1. What might be the full scope of Scheme 6 with respect to M? What about Pd, Pt, Rh, etc.? If other transition metals should participate in similar cross-coupling reactions, do they offer any synthetic advantages over Ni? Although Murahashi (56), Cassar (57), and Sonogashira (58) have reported some Pd-catalyzed cross-coupling reactions since 1975, at the outset of our investigation, this ability of Pd was unknown.
2. What might be the full scope of Scheme 6 with respect to M¹? Specifically, we hoped to be able to use B, Al, Si, Sn, and Zr. Organometallics containing these metals are known to be far more compatible with various electrophilic functionalities than those containing Li and Mg (1). More exciting to us was the possibility of generating stereo- and regiodefined alkenylmetals containing these metals *via* hydrometalation and carbometallation and transferring the alkenyl groups from metal to carbon.
3. What might be the full scope of Scheme 6 with respect to the R¹ and R² groups? Specifici-

cally, could we provide some solutions to many pending synthetic problems, such as development of selective alkenyl-alkenyl, alkenyl-allyl, and alkenyl-homoallyl coupling procedures?

(a) The palladium- or nickel-catalyzed cross coupling of two unsaturated organic groups.

Alkenyl-alkenyl coupling. In 1974 we began exploring the possibility of catalyzing the reaction of alkenylboranes or alkenylborates with organic halides using the Kumada-type Ni-phosphine complexes. Under mild reaction conditions we employed, the alkenylboron derivatives appeared totally unreactive. On the other hand, we found that the corresponding alkenylalanes reacted smoothly with aryl halides in the presence of a catalytic amount of $\text{Ni}(\text{PPh}_3)_4$ (59). This represents the first example of the use of organoalanes in the Ni-catalyzed cross coupling. We also noted the catalytic activity of $\text{Pd}(\text{PPh}_3)_4$ in this reaction. However, no special advantage of the Pd complex over the Ni complex was noted. Encouraged by the results, we then examined the Ni-catalyzed reaction of alkenylalanes with alkenyl iodides. We were pleased to find that the reaction of (*E*)-1-heptyldiisobutylalane (30) with (*E*)-1-iodo-1-hexene in the presence of 5 mol % of $\text{Ni}(\text{PPh}_3)_4$ gave the expected (*E,E*)-diene in 70% with 95% stereospecificity (eq 24) (60). Unfortunately, however, the stereospecificity observed in the reaction of 30 with (*Z*)-1-iodo-1-hexene was only 90% (eq 24).



The first indication that Pd-phosphine complexes might offer unique advantages over Ni-phosphine complexes was observed when the above alkenyl-alkenyl coupling reactions were run using a Pd-phosphine catalyst generated *in situ* by treating $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$ with 2 equivalents of *i*- Bu_2AlH (60). Although the product yields were comparable to those observed with the Ni catalyst, the stereospecificity in each case was > 99%.

The favorable results prompted a full-scale investigation of the Pd- or Ni-catalyzed cross coupling, which has been extensively reviewed elsewhere (61). The current scope of the Pd- or Ni-catalyzed cross coupling of two unsaturated groups is indicated in Table 1.

TABLE 1. Scope of the Pd- or Ni-catalyzed cross coupling of two unsaturated groups

| R^1 of R^1M | R^2 of R^2X | | Alkenyl | | Alkynyl | |
|-----------------|-----------------|----------------|---------|----------------|----------------|----------------|
| | Aryl | Ni | Pd | Ni | Pd | Ni |
| Aryl | + ^a | + | + | + | + | - ^b |
| Alkenyl | + | + | + | - ^c | + | - ^b |
| Alkynyl | + | - ^b | + | - ^b | - ^d | - ^b |

^a The + sign indicates satisfactory results. ^b The product yield is generally very low. ^c Stereochemical scrambling occurs. ^d Statistical mixtures of three diynes are formed in high combined yields.

The following generalizations may be presented as useful guidelines:

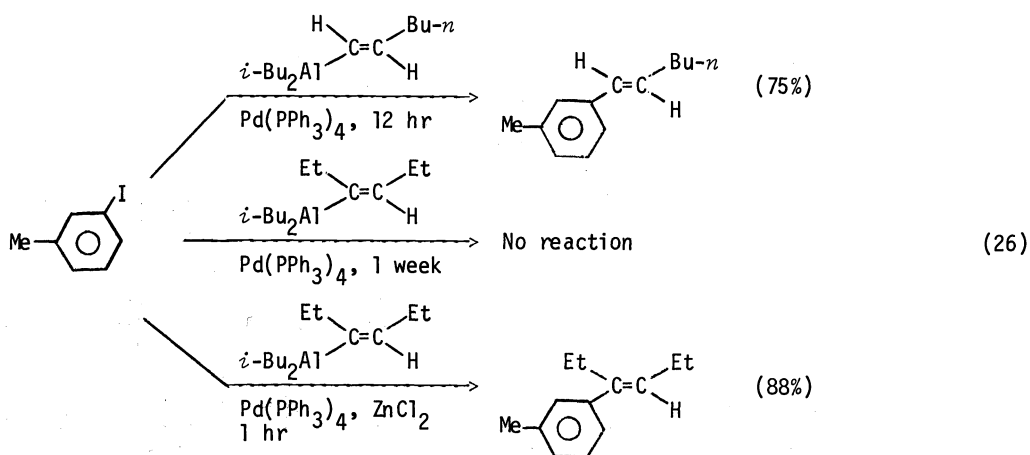
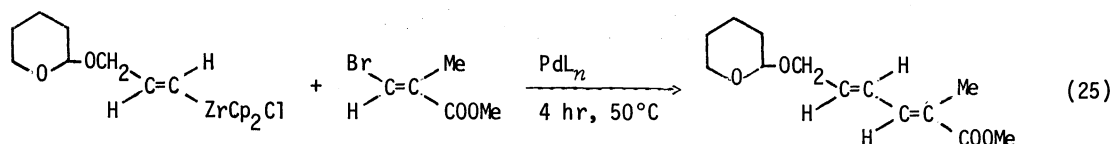
1. $\text{Ni}(\text{PPh}_3)_4$, which can be generated *in situ* by treating $\text{Ni}(\text{acac})_2$ with 2 equivalents of *i*- Bu_2AlH in the presence of 4 equivalents of PPh_3 , $\text{Pd}(\text{PPh}_3)_4$ and a Pd catalyst generated *in situ* by treating $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$ with 2 equivalents of *i*- Bu_2AlH are satisfactory catalysts.

2. Whereas organolithiums unexpectedly exhibit a low reactivity, alkenylmetals containing

Mg, Zn, Cd, Al and Zr, arylmetals containing Mg, Zn, Cd, and Al, and alkynylmetals containing Mg, Zn, Cd, B, Al, and Sn have been shown to participate in the Pd- or Ni-catalyzed cross coupling. In general, those containing Zn appear to be by far the most reactive and satisfactory class of organometallic reagents.

3. THF appears to be a highly satisfactory solvent in most cases.

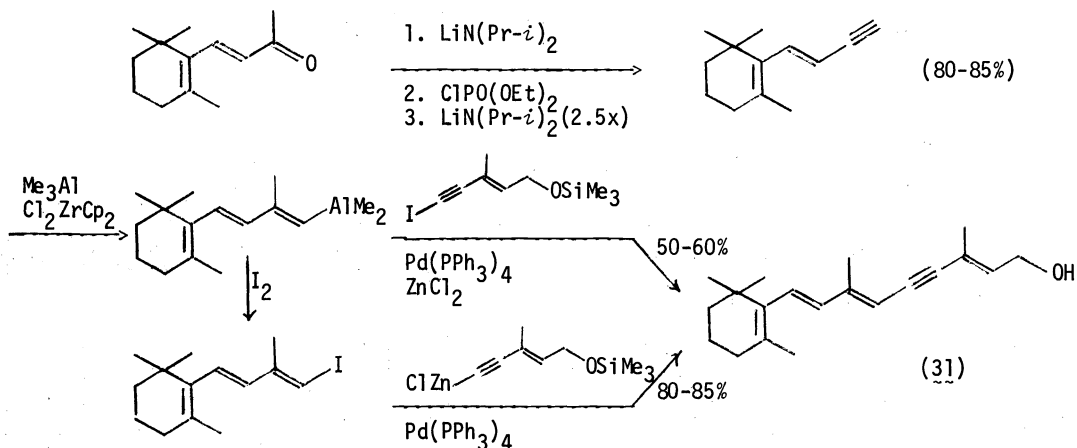
Having developed a seemingly general method for cross coupling unsaturated organometallics including alkenylalanes with unsaturated organic halides, such as alkenyl iodides, we proceeded to attempt a stereoselective synthesis of vitamin A. In light of highly satisfactory results obtained in the Pd- or Ni-catalyzed reaction of β -monosubstituted alkenylalanes (e.g., eq 24) (59, 60) and alkenylzirconium derivatives (e.g., eq 25) (62, 63), we were stunned by very disappointing results observed in similar reactions of α,β - or β,β -disubstituted alkenylalanes (e.g., eq 26) (64).



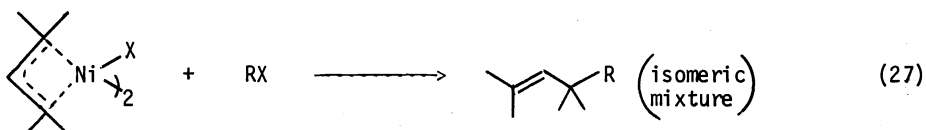
Fortunately, we soon found that the problem associated with the low reactivity of these sterically hindered alkenylalanes could be overcome by either adding $ZnCl_2$ as a co-catalyst (e.g., eq 26) (64) or converting the alkenylalanes into the corresponding iodides and using them as the halide components.

Using these improved procedures, dehydrovitamin A (31) has been synthesized as $\geq 98\%$ stereochemically pure substance (Scheme 7) (65).

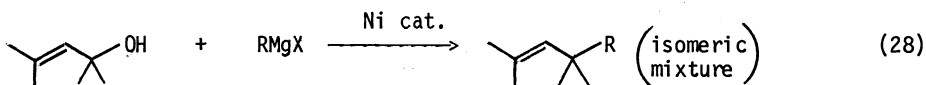
Scheme 7



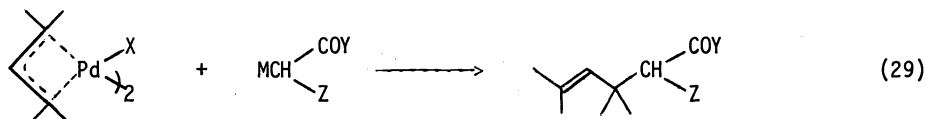
(b) The palladium-catalyzed allylation. A highly selective synthesis of 1,4-dienes. In 1967, Corey introduced the reaction of π -allylnickel derivatives with organic halides (eq 27) (66). The reaction, however, is not stereoselective with respect to the stereochemistry of the allylic halide.



A few years later, Felkin developed the Ni-catalyzed reaction of Grignard reagents with allylic alcohols (eq 28) (67). Although this reaction too is generally nonselective, it is unique in that it tends to involve attack by a Grignard reagent at the more hindered of the two equilibrating allylic carbon atoms.



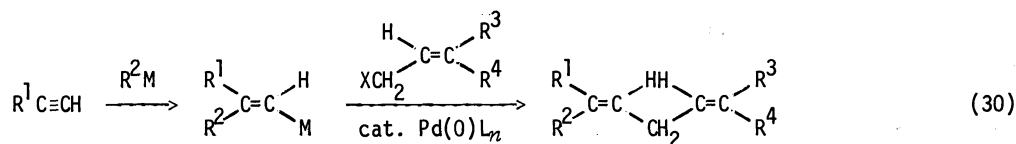
In 1965, Tsuji reported an allylation reaction with π -allylpalladium derivatives (68), which has been substantially refined and expanded by subsequent studies by Trost (eq 29) (69).



M = Alkali metal. Y = alkoxy or carbon group.
Z = COY, SO₂R, etc.

The reaction of π -allylpalladium derivatives appears to be more stereoselective than those of the π -allylnickel reactions. One serious drawback of the Pd-catalyzed allylation is that only certain types of enolates have been of use in the selective synthesis of complex molecules (69). Typical alkylmetals containing Li, Mg, Cu, etc. have been reported to be ineffective (69). A few relatively electronegative metals, such as Hg(70), Si(71), and Sn(72), have been reported to participate in the Pd-catalyzed allylation. However, their utility in the selective synthesis of olefins appears to be at best marginal.

Although the known results concerning the Pd-catalyzed allylation of organometallics were not encouraging, a large body of very favorable results we obtained in the Pd-catalyzed cross coupling prompted us to explore its full scope and synthetic utility. We have indeed found that the Pd-catalyzed reaction of alkenylmetals containing Al or Zr with allylic halides and various allylic alcohol derivatives can proceed with essentially complete retention of the stereo- and regiochemistry of both alkenyl and allyl groups (eq 30) (73).



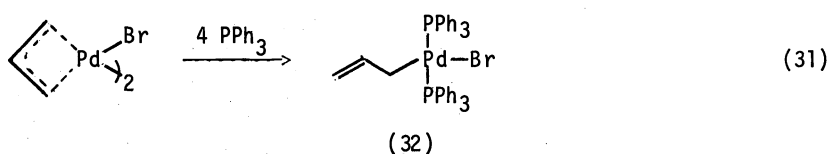
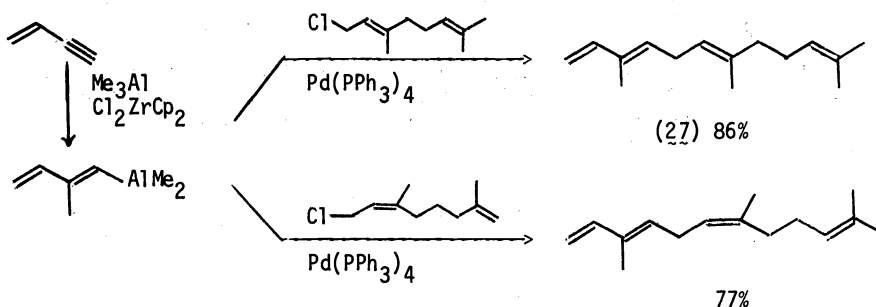
R¹ = carbon group. R² = H or alkyl. R³ and R⁴ = two hydrogens or two alkyl groups. M = Al or Zr.

When used in conjunction with the Zr-catalyzed carboalumination, the reaction provides a uniquely expeditious route to 1,4-dienes of terpenoid origin, as indicated by the following completely stereo- and regiospecific one-step synthesis of α -farnesene (27) and its 6Z-isomer (Scheme 8) (73).

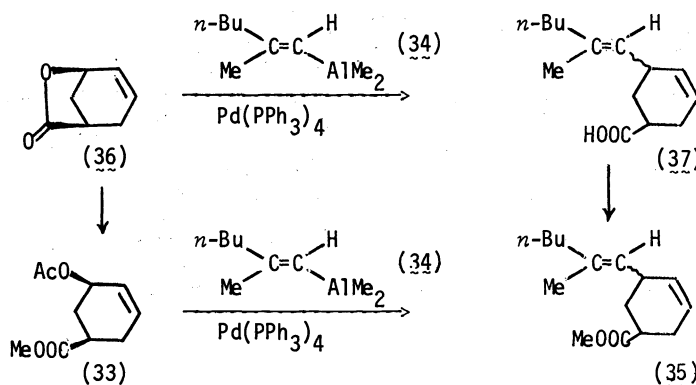
Treatment of the dimer of π -allylpalladium bromide (74) with 4 equivalents of PPh₃ (P/Pd = 2) has been reported to give σ -allylbromobis(triphenylphosphine)palladium (32) (75). The reaction of 32 with 1 equivalent of alkenylalanes is at least as fast as the corresponding catalytic reaction. It is therefore entirely possible that, unlike Trost's reaction of allylpalladium derivatives with "soft" carbanions which has been shown to involve the backside attack of π -allylpalladium cations by the carbanionic species (69), our reaction might involve attack of σ -allylpalladium derivatives, e.g., 32, by organometals *via* transmetalation which is followed by reductive elimination, as we have suggested for various other Pd-catalyzed cross-coupling reactions. To clarify this point, a cyclic allylic acetate (33) employed by Trost (76) was prepared and reacted with an alkenylalane (34) in the presence of 5 mol % of Pd(PPh₃)₄ to give an 85:15 mixture of 35 and its stereoisomer in essentially

quantitative combined yield. An essentially pure sample of **35** can be prepared by reacting a bicyclic lactone **36** with **34** to give **37**, which is then esterified to produce **35** (Scheme 9) (77). Since palladation of the allylic derivatives **33** or **36** is known to involve exclusive or predominant inversion, the transmetalation-reductive elimination sequence we propose should produce exclusively or largely the *trans* isomer. We are currently actively pursuing this problem.

Scheme 8

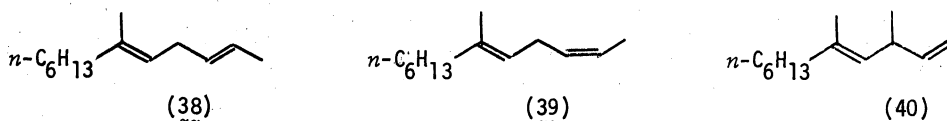


Scheme 9

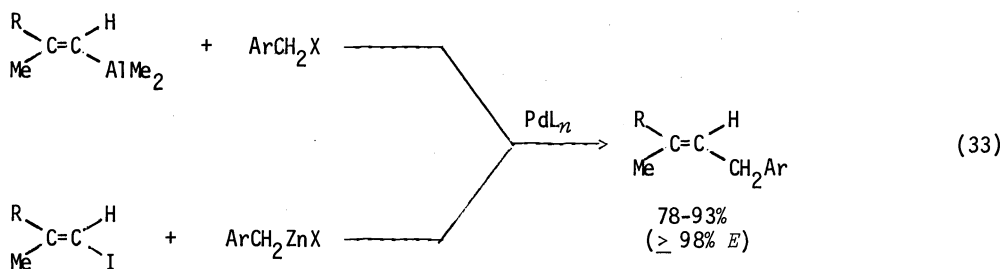
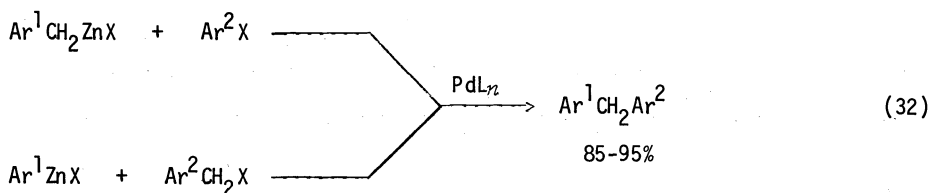


The Pd-catalyzed allylation has proved to be highly general with respect to the leaving group of the allylic derivatives. In addition to allylic halides and acetates, allylic alcohol derivatives containing OAlMe_2 , OPO(OEt)_2 , and OSiMe_3 groups can participate in the reaction, the order of their reactivity being: halogen, $\text{OAc} > \text{OAlMe}_2 > \text{OPO(OEt)}_2 > \text{OSiMe}_3$ (78).

Unlike γ,γ -nonsubstituted or γ,γ -disubstituted primary allylic derivatives, γ -monosubstituted allylic derivatives, such as crotyl acetate, react with partial scrambling of the regio- and stereochemistry of the allylic group. Typically, the Pd-catalyzed reaction of (*E*)-crotyl acetate with (*E*)-(2-methyl-1-octenyl)dimethylalane give an 80:10:10 mixture of **38**, **39**, and **40** (78) (79).



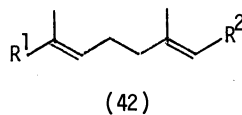
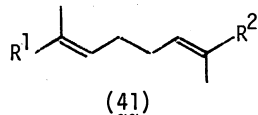
We have also found that the Pd catalysis is highly effective in the synthesis of diaryl-methanes (eq 32) (80) (81) and allylated arenes (eq 33) (81). The allylated arene syntheses shown in eq 33 promise to provide selective routes to various natural products including vitamins K (82), coenzymes Q (82) and maytansinoids (83).



In summary, a wide variety of 1,4-dienes, diarylmethanes, and allylated arenes can now be synthesized often in a nearly completely selective manner by the Pd-catalyzed cross coupling. All of these reactions are indeed significantly catalyzed by Pd-phosphine complexes. Although diarylmethanes and simple allylated arenes may also be prepared using Ni complexes, Pd-phosphine complexes show distinct advantages over Ni complexes with respect to stereo- and regioselectivity. A related recent study of allylation by Schwartz (79) and a mechanism-oriented study of benzylation by Stille (84) should be mentioned here, although presentation of their results is beyond the scope of this review.

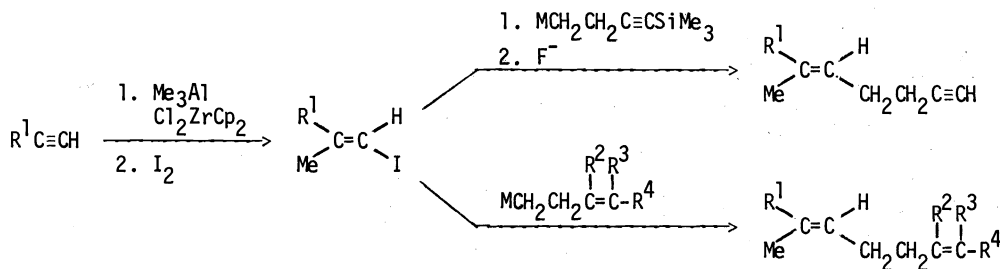
(c) The palladium-catalyzed alkylation. An efficient and selective synthesis of 1,5-enynes and 1,5-dienes. One of the major disadvantages of the Pd- or Ni-catalyzed cross coupling relative to the Cu-promoted cross coupling (3) is that alkyl halides containing β hydrogens cannot be utilized, presumably because their oxidative addition with Pd(0) or Ni(0) complexes is accompanied by β -elimination of the resultant alkylmetal derivatives. Indeed, the same β -elimination is supposedly the product-forming step in the Pd-promoted Heck reaction (85). These negative facts indeed delayed our investigation of the Pd-catalyzed alkylation. In connection with our study directed toward the development of 1,5-diene syntheses, however, it became desirable to develop satisfactory methods for alkenyl-homoallyl or alkenyl-homopropargyl coupling.

Construction of 1,5-diene units present in various natural products of terpenoid origin, such as 41 and 42, *via* cross coupling has been achieved in most cases by the Biellmann and related allyl-allyl coupling reactions (86).



While these reactions appear well suited for synthesizing the head-to-head 1,5-dienes (41), their application to the synthesis of 42 is often complicated by regioscrambling and other side reactions (87). Although we have recently developed a three-step route to 1,5-enynes *via* allyl-propargyl coupling (eq 19) (45), the following two-pot procedure *via* alkenyl-homoallyl or alkenyl-homopropargyl coupling appeared particularly attractive in view of the ready availability of the required alkenyl iodides (30).

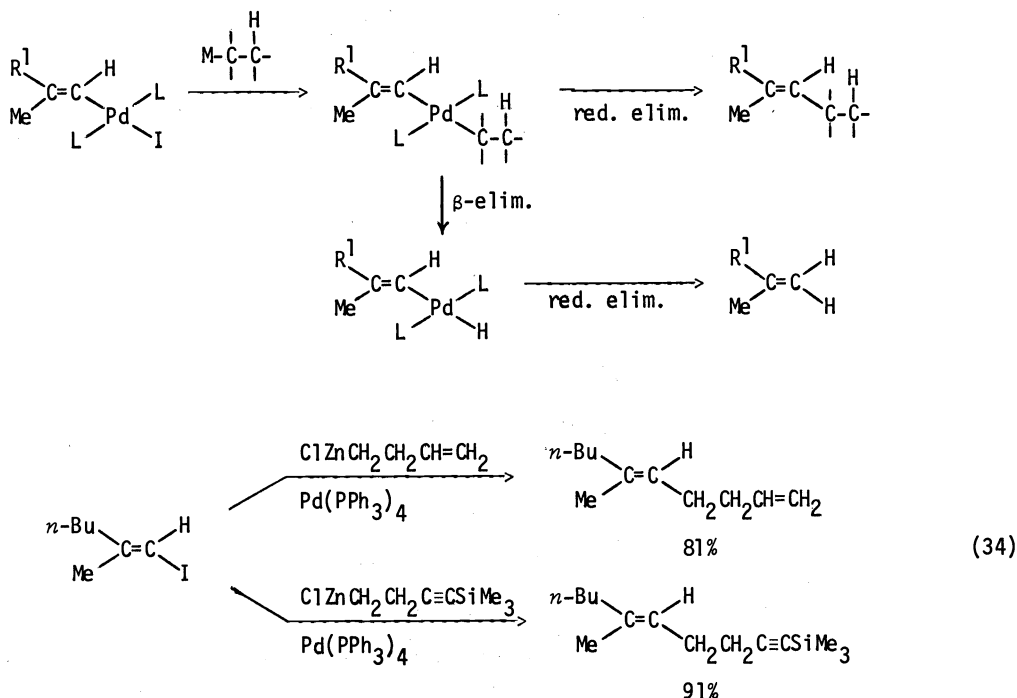
Scheme 10



We reasoned that, if transmetalation of alkylmetals containing β -hydrogens as well as subsequent reductive elimination were substantially faster than β -elimination of alkylpalladium intermediates, Pd complexes can be effective catalysts for alkylation (Scheme 11).

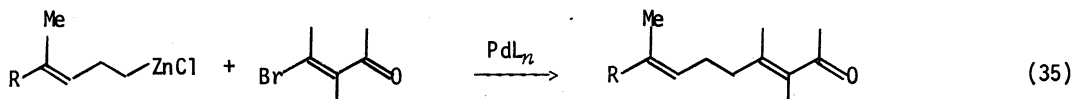
We were very pleased to find that both homoallylzinc chloride and 4-trimethylsilyl-3-butynyl-zinc chloride underwent a Pd-catalyzed coupling reaction with (*E*)-1-iodo-2-methyl-1-hexene to give the corresponding coupled products in 81 and 91% yields, respectively (eq 34) (41). The extent of β -elimination as judged by the amount of the deiodinated alkene was < 1-2% in each case.

Scheme 11

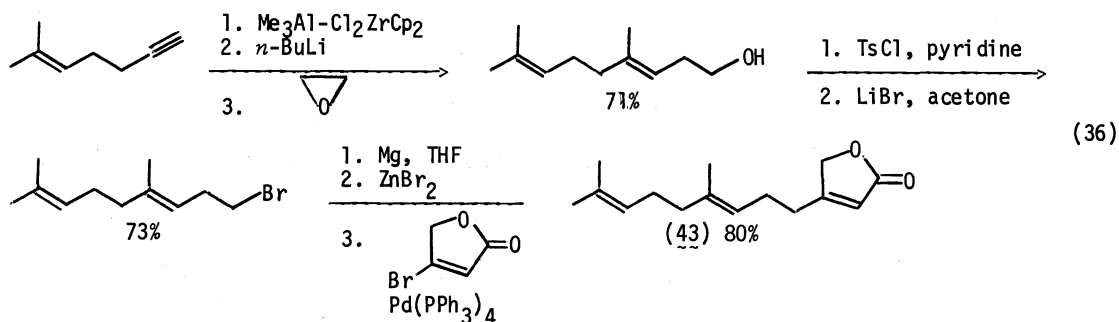


After completion of this study, we were informed of a related alkylation study by Kumada (88). Should these reactions proceed as shown in Scheme 11, the observed results then indicate that reductive elimination can proceed far faster than β -elimination even in cases where the latter process involves removal of an allylic or propargylic hydrogen atom.

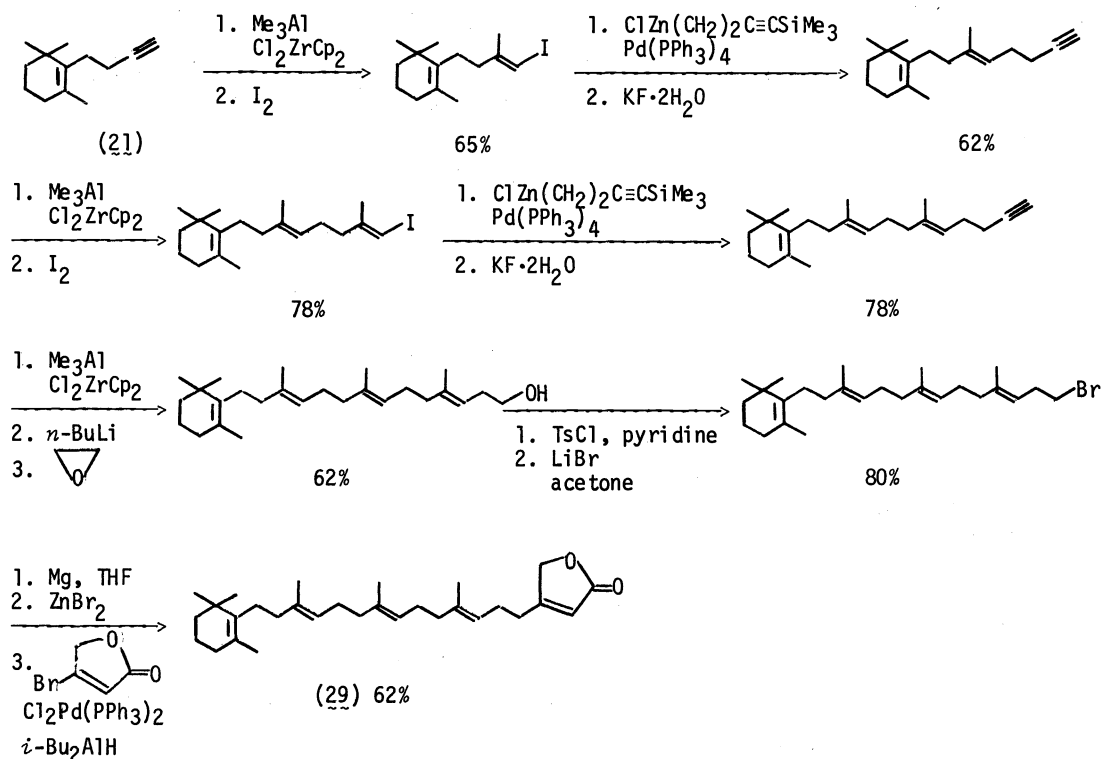
The Pd-catalyzed reaction of alkylzinc derivatives is compatible with the use of stereodefined homoallyl groups and β -carbonyl substituted alkenyl halides so as to effect the "conjugate substitution" reaction shown in eq 35 (89).



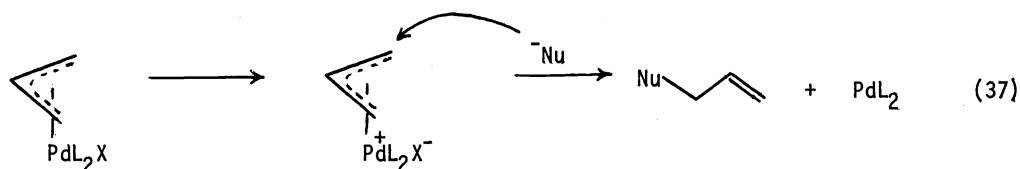
The Zr-catalyzed carboalumination of acetylenes and the Pd-catalyzed alkenyl-homoallyl or alkenyl-homopropargyl coupling can now be combined to develop efficient and selective synthetic schemes for a variety of terpenoids. All of these reactions are > 98% stereospecific and/or stereoselective. Furthermore, the Pd-catalyzed reactions shown in eqs 34 and 35 are totally regioselective. Only the Pd-catalyzed carboalumination usually produces ~ 5% of the undesirable regioisomers. The regioisomeric impurities are readily separable in most cases. Furthermore, the undesired regioisomers in the carboalumination products are considerably less reactive than the desired regioisomers in many subsequent reactions, presumably due to the greater steric hindrance around Al. As a result, \geq 98% isomerically pure products are often obtained without isomer separation. The following syntheses of a precursor **43** of dendrolasin (**28**) and mokupalide (**29**) are representative of such highly stereo- and regioselective procedures (eq 36 and Scheme 12) (41 and 89). Reduction of **43** with *i*-Bu₂AlH has been reported to give **28** in 85-95% yield (90).



Scheme 12

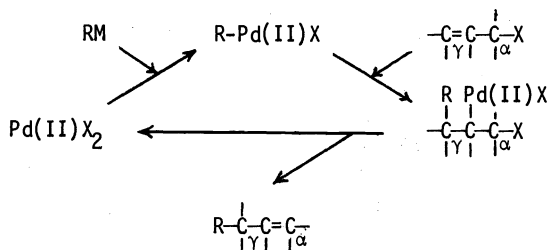


Before closing this section it seems appropriate to discuss several distinct mechanisms that might be operating in the Pd-catalyzed cross coupling. In addition to (i) the oxidative addition-transmetalation-reductive elimination scheme that we have proposed for various Pd-catalyzed cross-coupling reactions involving relatively electropositive metals, e.g., Mg, Zn, and Al (50), as well as (ii) a rather special π -allylpalladium cation mechanism of Trost (eq 37) (69), which is applicable only to the allylation cases, two distinct addition-elimination mechanisms originally proposed by Heck (85) have been used to explain observed results, although none appears to have been fully established.



The Heck mechanisms are applicable only in cases where α,β - or β,γ -unsaturated organometals and/or organic electrophiles, e.g., alkenyl, alkynyl, allyl, and propargyl derivatives, are used. One of them, which might be termed the Heck Type I mechanism involves a transmetalation-addition-elimination sequence as exemplified by Scheme 13.

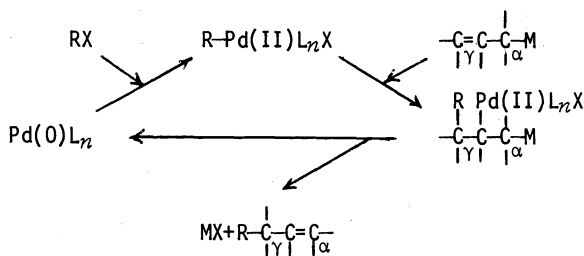
Scheme 13



A few critical differences between this mechanism and the one we have proposed should be noted. First, neither oxidation nor reduction of Pd is involved in Scheme 13. Second, the C=C bond is temporarily destroyed and the allylic system undergoes an allylic rearrangement in Scheme 13, while neither is required in our mechanism proposed earlier for eq 30.

The other addition-elimination mechanism is an adaptation of a mechanism proposed by Heck for the Pd-catalyzed reaction of organic halides with olefins and acetylenes. This mechanism applies to those cases where α,β - or β,γ -unsaturated organometals are involved. The Pd-catalyzed reaction of allylmetals, for example, may be represented by Scheme 14.

Scheme 14

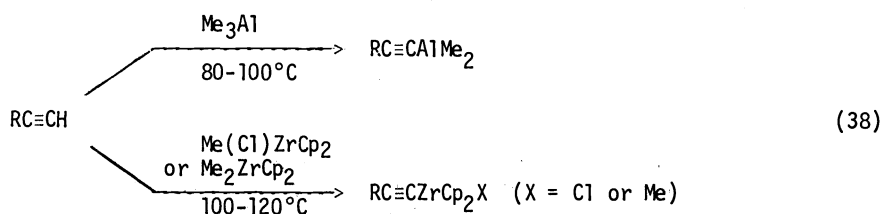


We have earlier proposed the alkynylmetal version of this mechanism (5). Although it is not explicitly proposed, the Pd-catalyzed allylation reaction of allyltins (72) can be explained by this mechanism. Here again, the C=C bond is temporarily destroyed and an allylic rearrangement occurs.

The currently available data indicate that all of these mechanisms probably operate in various Pd-catalyzed cross-coupling reactions. Aside from a rather special mechanism of Trost (eq 37), the Heck-type mechanisms seem to be favored by relatively electronegative metals, while the oxidative addition-transmetallation-reductive elimination mechanism appears to be favored by more electropositive metals. From the synthetic point of view the Pd-catalyzed cross coupling involving relatively electropositive metals, which appears to proceed by the oxidative addition-transmetallation-reductive elimination mechanism, is characterized by its high stereo- and regioselectivity as well as its general applicability.

MECHANISM OF THE ZIRCONIUM-CATALYZED CARBOALUMINATION

The Zr-catalyzed carboalumination of acetylenes shown in eq 9 displays features which initially led us to suggest that the reaction might involve an Al-assisted carbozirconation in the crucial carbon-carbon bond-forming step. It should be emphasized at the outset of our discussion that the reaction shown in eq 9 requires both Al and Zr reagents. Thus, no reaction occurs under otherwise comparable reaction conditions, if a terminal acetylene, e.g., 1-heptyne, is reacted either with only Me_3Al in the absence of Cl_2ZrCp_2 or with preformed $\text{Me}(\text{Cl})\text{ZrCp}_2$ or Me_2ZrCp_2 in the absence of any Al reagent. Moreover, if either of the above reaction mixtures is heated to around 100°C or above, the major course of reaction is abstraction of the acetylenic hydrogen to form alkynylmetals (eq 38) (19).

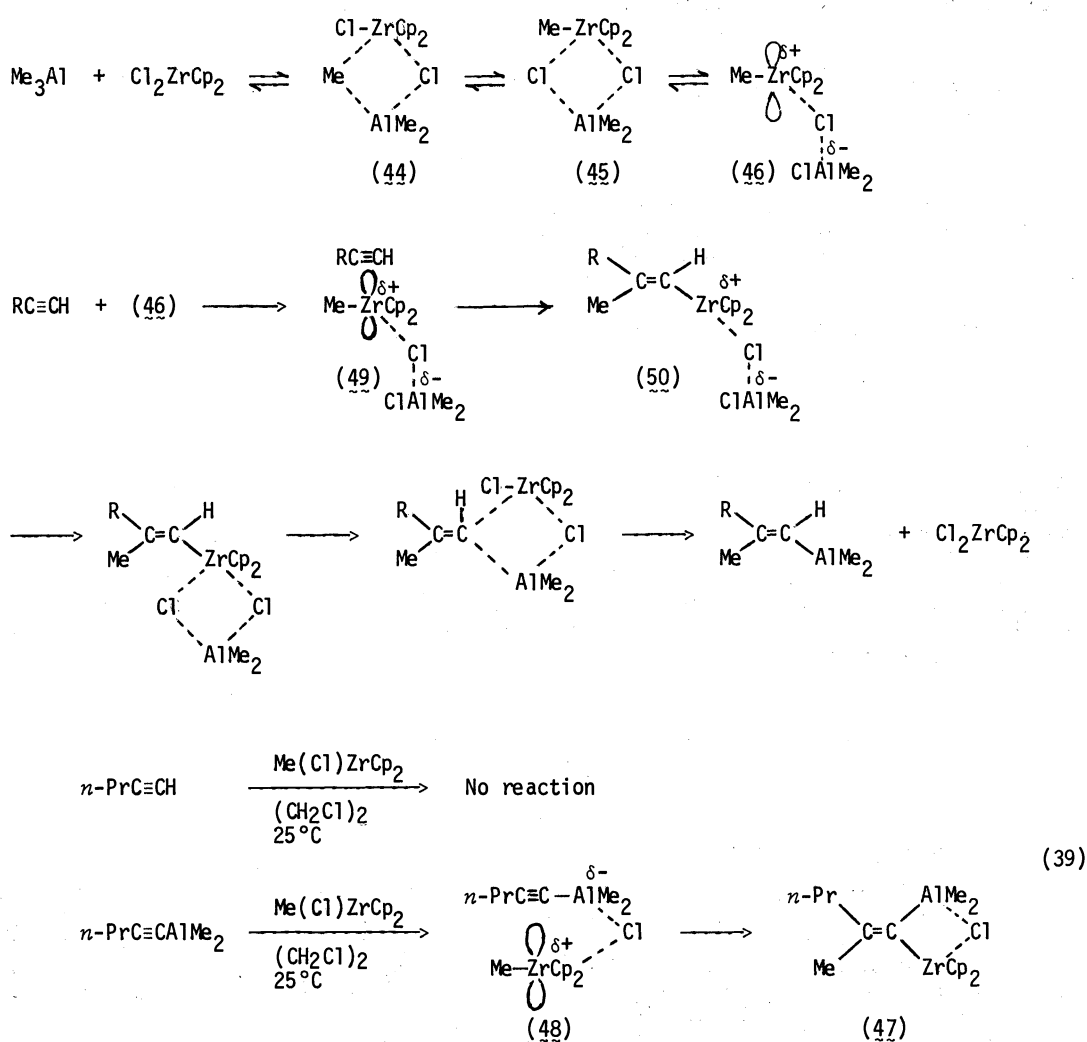


The simultaneous presence of Al and Zr reagents clearly indicates that the reaction must in-

volve an Al-assisted carbozirconation and/or a Zr-assisted carboalumination in the crucial step.

Some of our findings that favor the Al-assisted carbozirconation mechanism, e.g., Scheme 15, are as follows. First, Me_3Al and Cl_2ZrCp_2 undergo a Me-Cl exchange to form species containing the $\text{Me}(\text{Cl})\text{ZrCp}_2$ moiety, such as **44** and **45**, which is rapid on the NMR time scale at ambient temperature (19)(26). Cleavage of a bridging Zr-Cl bond in **45** would give a Me-Zr bonded species (**46**) which might be expected to be highly reactive toward acetylenes due not only to the presence of an empty coordination site but to the partial positive charge on the Zr atom. Second, the reaction of a 1-alkynyl dimethylalane, e.g., $n\text{-PrC}\equiv\text{CAI}\text{Me}_2$, with Al-free $\text{Me}(\text{Cl})\text{ZrCp}_2$ (**91**) in a 1:1 ratio gives cleanly and quantitatively the carbozirconation product (**47**), thereby providing a clean-cut example of carbozirconation of acetylenes (eq 39) (92). It should be emphasized here again that no reaction is observed between 1-pentyne itself and $\text{Me}(\text{Cl})\text{ZrCp}_2$ under comparable conditions. An Al-Zr species (**48**), similar to **49** in Scheme 15, appears to be a plausible active species for this particular reaction. Third, alkenylchlorobis(π -cyclopentadienyl)zirconium species are known to be readily converted into the corresponding alkenylalanes on treatment with suitable alanes (25), thereby providing a possible mechanism for *in situ* conversion of the alkenylzirconium species (**50**) into alkenylalanes.

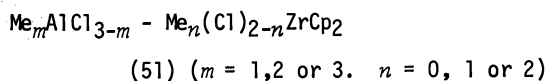
Scheme 15



Despite all these facts and interpretations, our more recent results indicate that, while the Al-assisted carbozirconation mechanism may still be correct for the case shown in eq 39, the reaction of typical terminal acetylenes with Al-Zr reagent systems must involve a Zr-assisted carboalumination.

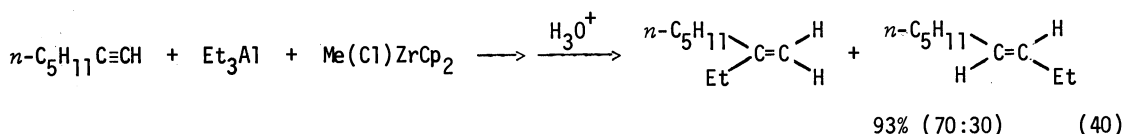
In the hope of clarifying mechanistic details of the Zr-catalyzed carboalumination, we have

varied m and n in the reagent systems (51) and examined their ^1H NMR (-50 to 80°C) as well as their reaction with 1-heptyne.

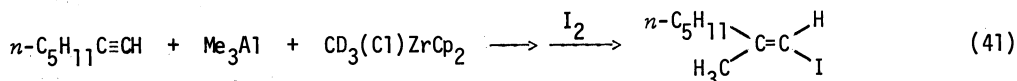


Of the five Al-Zr reagent systems studied, all except the $\text{MeAlCl}_2\text{-Cl}_2\text{ZrCp}_2$ system undergo the expected carbometallation. Although the yield of the protonolysis product observed with $\text{Me}_2\text{AlCl-Cl}_2\text{ZrCp}_2$ was only 65% (after 48 hr), the other three reactions proceeded quantitatively within 24 hr, the order of reactivity being: $\text{Me}_3\text{Al-Cl}_2\text{ZrCp}_2 \sim \text{Me}_3\text{Al-Me}(\text{Cl})\text{ZrCp}_2 > \text{Me}_3\text{Al-Me}_2\text{ZrCp}_2 > \text{Me}_2\text{AlCl-Cl}_2\text{ZrCp}_2$ (26). Of the four reagent systems that undergo the expected carbometallation, only the $\text{Me}_3\text{Al-Cl}_2\text{ZrCp}_2$ system shows a rapid Me-Cl exchange. All the other systems do not undergo a Me-Cl exchange which is rapid on the NMR time scale at ambient temperature (26). These results clearly indicate that the rapid Me-Cl exchange, which was considered as a crucial step in Scheme 15, is not required for the carbometallation.

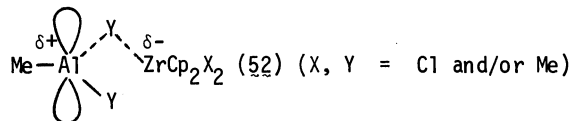
To further probe the critical question of Al-assisted carbozirconation *vs.* Zr-assisted carboaluminum, we have reacted 1-heptyne with a 1:1 mixture of Et_3Al and $\text{Me}(\text{Cl})\text{ZrCp}_2$ and found that the reaction produces, after protonolysis, a 70:30 mixture of 2-ethyl-1-heptene and (*E*)-3-nonene in 93% combined yield with only traces, if any, of the corresponding methylated alkenes (eq 40) (26). The results are not only consistent with direct carboaluminum but inconsistent with direct carbozirconation.



To rule out any special effect, if any, due to the difference between Me and Et, we have then run the reaction of 1-heptyne with a 1:1 mixture of Me_3Al and $\text{CD}_3(\text{Cl})\text{ZrCp}_2$, prepared by the reaction of Cl_2ZrCp_2 with 2 equivalents of CD_3MgI in ether followed by treatment with 1.5 equivalents of PbCl_2 in benzene. The product obtained in essentially quantitative yield after iodination is 98% pure (*E*)-1-iodo-2-methyl-1-heptene contaminated with 2% of (*Z*)-3-iodo-2-octene. The extent of D incorporation is < 4% (eq 41) (26).



Although the precise role of Zr reagents remains to be unclear, we may now conclude that the Zr-catalyzed carboaluminum of terminal acetylenes, at least in some typical cases, proceeds by a Zr-assisted carboaluminum. The results of the mechanistic study suggest that, while the Al-Zr combination may well be best suited for addition of the methyl-metal bond to the C=C bond, other metals may also be capable of activating the C-Al bond toward acetylenes. Our preliminary results also indicate that organozincs can also participate in the Zr-promoted carbometallation (19). As to the actual reactive species in the Zr-catalyzed carboaluminum, we can only suggest an Al-Zr species (52).



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