Principle of Activation of Electrophiles by Electrophiles through Dimeric Association—Two Are Better than One

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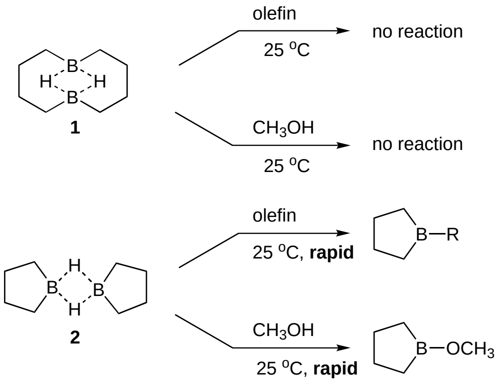
This paper is dedicated to Professors Herbert C. Brown and George A. Olah in recognition of their pioneering studies in the general area of Lewis acid catalysis

Abstract: Electron-deficient metal compounds can be significantly activated as electrophiles through dimeric (or polymeric) association with either the same or different electrophiles. Although this phenomenon has played an important role in many reactions, such as the Friedel–Crafts reaction and the Ziegler–Natta polymerization, it has apparently only recently been fully recognized. Its widespread exploitation promises to lead to many new synthetically useful reactions as well as ready and accurate interpretations of mechanistic and structural phenomena in acid-catalyzed and -promoted reactions.

Keywords: aluminum • dimerization • electron deficiency • Lewis acids • zirconium

Introduction

Metals can readily provide electron-deficient species. Thus, trialkylboranes tend to exist as monomeric 6-electron species,[1] and 16-electron species containing transition metals are also electron-deficient.[2] As such, they can serve as Lewis acids in both stoichiometric and catalytic manners. At the same time, however, they have a strong tendency to plug up their empty orbitals through dimerization and polymerization. Boron hydrides, including diborane (B_2H_6), essentially all mono- and dialkylboranes,[3, 4] and trialkylalanes[5] are known to exist as doubly bridged dimers. Many higher oligomeric and polymeric aggregates are also known.[6] In cases where all valence-shell empty orbitals are plugged, such coordinatively saturated species may not readily serve as Lewis acids. For example, coordinatively saturated B_2H_6 needs to be heated above 100 °C for its hydroboration with ethylene,[7] and dimeric dialkylboranes are believed to dissociate into monomers for their hydroboration with alkenes.[8] A striking contrast between 1,6-diboracyclodecane (**1**),[9] which cannot readily dissociate into a monomeric dialkylborane, and its more elusive isomer bisborolane (**2**)[10] shown in Scheme 1 clearly supports dissociative mechanisms. These and other related findings have provided the basis for a well-accepted and useful notion that might be termed **the principle of activation of Lewis acids or electrophiles through dissociation.** In short, one is better than two.



Scheme 1. Striking contrast in reactivity between 1,6-diboracyclodecane and bis(borolane).

Much less well known is a seemingly contradictory concept or generalization that might be termed **the principle of activation of Lewis acids or electrophiles through association**. As is clear from the discussion presented above, coordinatively unsaturated monomers (**3**) are far more Lewis acidic than doubly bridged coordinatively saturated dimers (**4**). However, the same compound can, in principle, readily generate a species that is even more Lewis acidic than the monomer through the formation of a singly bridged dimer (**5**). In **5** the electron-deficient metal center is clearly more Lewis acidic than that in **3**. Generation of **5** must be occurring in a dynamic monomer–dimer equilibrium, and it should be a widely observable phenomenon. Such an associative interaction may also be observable between two or more different metal-containing species.[11] In an extreme situation, polar-

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ization of the M–X bond may lead to its full ionization to generate an ion pair; this is thought to be important in Ti- and Zr-catalyzed alkene polymerizations.[12, 13] Clearly, the relative acidity or electrophilicity of various monomeric and dimeric species of M–X is: **6** > **5** > **3** > **4**, as illustrated in Figure 1. If the monomer **3** is a 6- (or 16-) electron species, **6**, **5**, and **4** are respectively 4- (or 14-), 6- (or 16-), and 8- (or 18-) electron species. However, distinction among these species, especially that between **5** and **6**, can be subtle. In this article, attention is mainly focused on the contrast between **3** and **5** with special emphasis on heterobimetallic interactions.

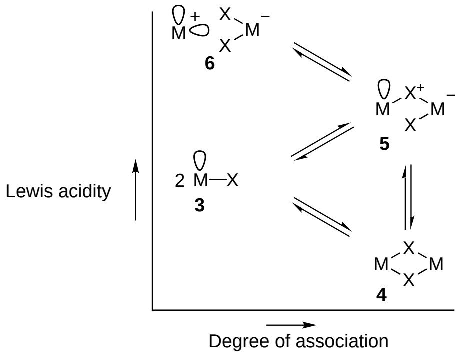


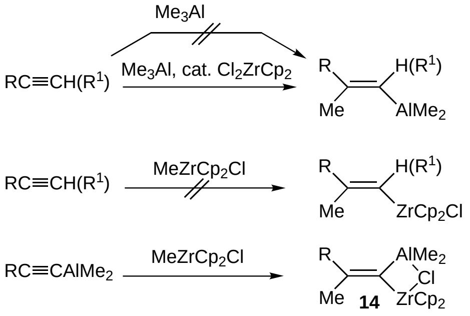
Figure 1. Relationship between Lewis acidity and state of association of M–X.

Discussion

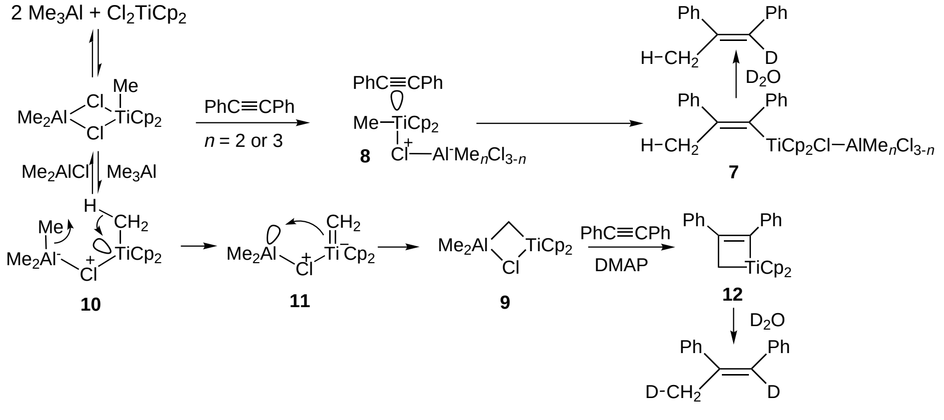
Carbotitanation with Ti–Al reagents and Ti-catalyzed carboalumination: The simplistic concept presented in Figure 1 led to the discovery in 1978 of the methyltitanation of diphenylacetylene with $2\,Me_3Al–Cp_2TiCl_2$ in high yield involving essentially 100% *syn* addition.[14] The stoichiometric nature of the reaction with respect to Ti suggested that the product might be an alkenyltitanium species **7**, but this point was clarified only in 1997,[15] and the process was interpreted in terms of an Al-assisted methyltitanation (**8**) (Scheme 2). It is interesting to note that in 1978 $2\,Me_3Al–Cp_2TiCl_2$ was also independently reported to give the Tebbe reagent (**9**) slowly by α C–H activation,[16] which was later shown to involve a bimetallic intramolecular acid–base interaction (**10** and **11**).[17] Treatment of the Tebbe reagent with a base, such as 4-(*N*,*N*-dimethylamino)pyridine (DMAP), is known to produce methylenetitanocene, which reacts with PhC≡CPh to give the corresponding titanacyclobutene (**12**).[16b] The dichotomy exhibited by the acyclic and cyclic processes (Scheme 2) was initially puzzling, but both results have been compellingly confirmed. Within the context of the present discussion, the associative bimetallic interactions in **8** and **10** are important. Under comparable conditions $MeTiCp_2Cl$ alone does not react with PhC≡CPh, so both Ti and Al are needed at the crucial moment.

Although the carbotitanation reaction shown above was only stoichiometric with respect to both Ti and Al[15] and rather limited in scope with respect to both π compounds and the alkyl group, some Ti-catalyzed carboalumination reactions of alkenes[18] and dienes as well as higher polyenes[19] using Ti^{IV} alkoxides without Cp have been recently developed.

Zirconium-catalyzed carboalumination of alkynes: The limited scope and the stoichiometric nature of the carbotitanation of alkynes prompted screening of the other members of the Ti triad, and it was discovered also in 1978 that the reaction of Me_3Al and Cl_2ZrCp_2 with alkynes was not only quite general with respect to the alkyne structure but also catalytic in Zr. Thus, it leads to carboalumination, that is, net addition of a C–Al bond to an alkyne.[20] As expected from an assumption that the reaction would be concerted, essentially 100% *syn* addition has been observed. Here again, it should be stressed that neither Me_3Al nor preformed $MeZrCp_2Cl$ would react with alkynes under the same conditions (Scheme 3). The results strongly suggested some bimetallic process, and the Al-assisted carbozirconation mechanism involving **13** (Scheme 4) has been supported by various observations including rapid Me–Cl exchange between Me_3Al and Cl_2ZrCp_2 observed by NMR spectroscopy[21] and a facile methylzirconation of dimethylalumino-substituted alkynes to give **14**[22] (Scheme 3). However, the reaction must be multimechanistic. Thus, Me_2AlCl has been shown not



Scheme 3. Zirconium-catalyzed methylalumination of alkynes and methylzirconation of $RC≡CAlMe_2$.



Scheme 2. Titanium-catalyzed carboalumination of PhC≡CPh with $2\,Me_3Al–Cl_2TiCp_2$.

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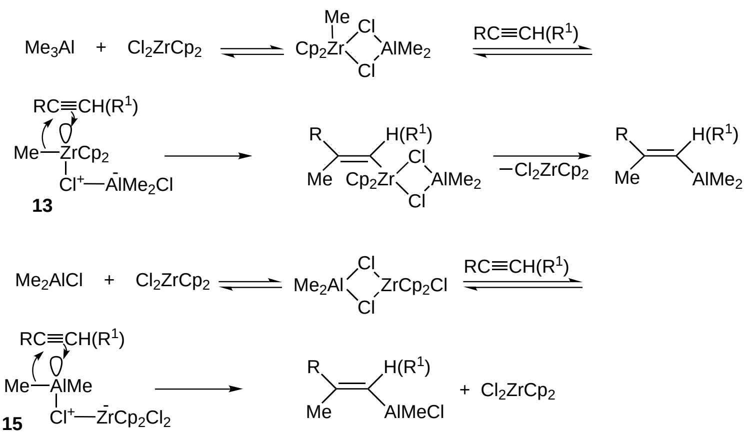
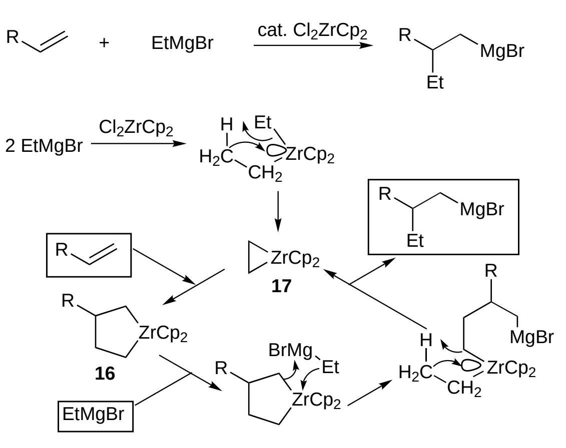


Scheme 4. Dichotomous four-center addition mechanisms for zirconium-catalyzed methylalumination of alkenes.

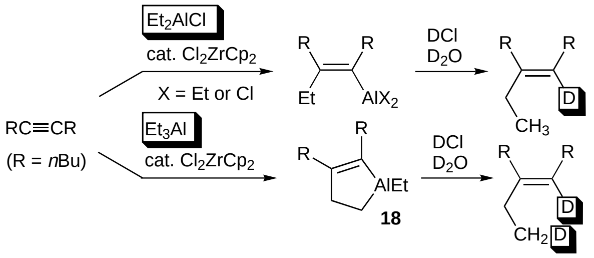
to transfer Me onto Cl_2ZrCp_2.[21] And yet, it undergoes a relatively smooth Zr-catalyzed methylalumination of alkynes[20, 21] (Scheme 4). Furthermore, the use of Et_2AlCl and higher dialkylchloroalanes is not complicated by competitive hydroalumination, which is a serious side reaction with Et_3Al and higher trialkylalanes containing β hydrogen atoms. For the reactions of dialkylchloroalanes, a mechanism involving direct C–Al bond addition assisted by Zr, shown in **15**, has been proposed (Scheme 4).[21, 23] As might be expected, Zr-catalyzed allylalumination and benzylalumination of alkynes proceed well.[24] Zr-catalyzed carbozincation of alkynes with Et_2Zn[25] and diallylzinc[26] have also been developed in conjunction with I_2ZrCp_2, which is more reactive than Cl_2ZrCp_2.

The scope of the Zr-catalyzed carboalumination did not initially include alkenes as substrates. Several years later, however, a similar Zr-catalyzed ethylmagnesation of terminal alkenes using EtMgBr and Cl_2ZrCp_2 was reported.[27] Puzzlingly, methylmagnesium reagents would not participate in the reaction. A four-center addition mechanism similar to those shown in Scheme 4 was initially suggested. However, in 1991 the reaction was unexpectedly shown to proceed by a multistep catalytic cycle involving β C–H activation[28] (Scheme 5). Fortunately, each of the steps in the catalytic cycle was stoichiometrically observable, and the key to the mechanistic clarification was the finding that zirconacyclopentanes (**16**) react with EtMgBr by σ-bond metathesis and β C–H activation to give the ethylmagnesation product and ethylene–$ZrCp_2$ (**17**)[28] which was not clarified in independently reported other mechanistic suggestions.[29] Failure to achieve methylmagnesation is readily explained by the absence of a β C–H bond in Me. Significantly, this mechanistic clarification posed a serious general question as to whether or not other Zr-catalyzed carbometalations with Et and other β-C–H-containing alkyl groups might also proceed by cyclic mechanisms.



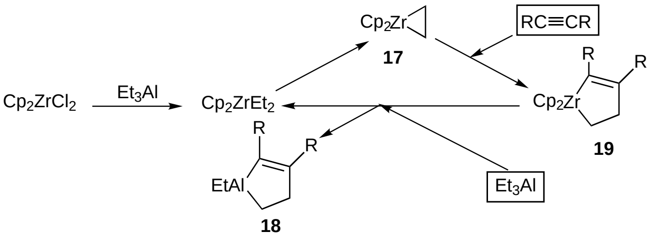
Scheme 5. Cyclic mechanism for the Dzhemilev ethylmagnesation of alkenes.

In view of the concern described above, the Zr-catalyzed reaction of higher alkylalanes with alkynes was reinvestigated using 5-decyne as the representative substrate. Very surprisingly, the reaction of Et_3Al, which earlier was thought to involve simple four-center addition to alkynes,[20, 21] was strictly a cyclic process giving **18**, which interestingly was favored by nonpolar solvents such as hexanes. When Et_2AlCl was used in place of Et_3Al, however, the reaction proceeded more readily in more polar solvents like CH_2Cl_2 without showing any sign of cyclization[23] (Scheme 6). These reactions require both Al and Zr reagents. As Et_2AlCl shows no sign of Et–Cl exchange with Cl_2ZrCp_2, a Zr-assisted direct carboalumination mechanism similar to that involving **15** shown in Scheme 4 may be proposed for the reaction. The next question was how the cyclic carboalumination might proceed.

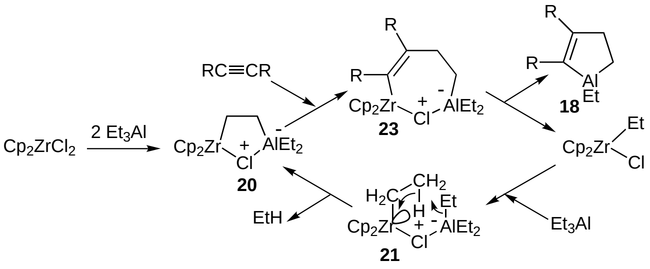


Scheme 6. Dichotomy in zirconium-catalyzed ethylalumination of 5-decyne.

Its clarification proved to be a major challenge. In the light of the mechanism of the Dzhemilev reaction (Scheme 5), a similar mechanism involving the intermediacy of a zirconacyclopropane **17** and a zirconacyclopentene **19** was considered first (Scheme 7). However, it was soon ruled out since there was no indication of diethylation of Cl_2ZrCp_2 with Et_3Al from NMR spectroscopy and since **19**, prepared by the reaction of 5-decyne with EtMgBr (2 equiv) and Cl_2ZrCp_2[30] and therefore free of Al, did not induce the indicated catalytic cycle in the presence of a 1:1 mixture of 5-decyne and Et_3Al.[23]

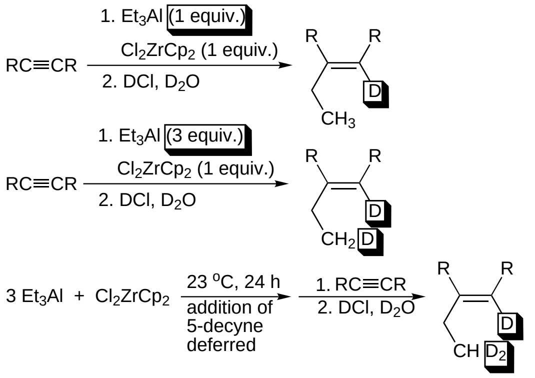


Scheme 7. Initially considered, erroneous mechanism for zirconium-catalyzed cyclic ethylalumination of 5-decyne.

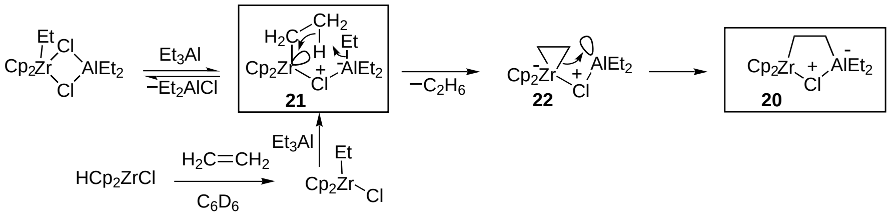


Scheme 11. Proposed mechanism for the zirconium-catalyzed reaction of 5-decyne with Et_3Al.

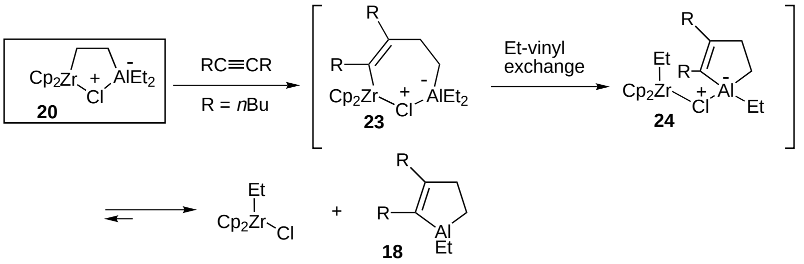
Eventually, the three sets of results of pertinent stoichiometric reactions shown in Schemes 8–10 were put together to come up with a most intricate bimetallic catalytic cycle, shown in Scheme 11.[23] Equally crucial was the recognition of a striking parallel between the previously reported results of a series of structural studies without the involvement of alkynes[31, 32] and the three stoichiometric reactions of 5-decyne with Et_3Al and Cl_2ZrCp_2 under three different conditions. The formation of the catalytically important intermediate **20** was shown to occur more readily and more cleanly by the reaction of Et_3Al with $EtZrCp_2Cl$, generated by treatment of ethylene with $HZrCp_2Cl$. The results support the notion that Et_2AlCl must be temporarily displaced by Et_3Al for crucial bimetallic β C–H activation via **21** and **22** for the generation of **20**, which has been fully characterized spectroscopically and chemically. In the absence of an excess of Et_3Al, as in the 1:1 Et_3Al–Cl_2ZrCp_2 reaction, no β C–H activation occurs, and only straightforward four-center carbometalation is possible. As expected, **20** reacts readily with 5-decyne under the stoichiometric conditions. The initial carbozirconation product must be **23**. However, it evidently undergoes subsequent alkenyl–Et exchange to give free $EtZrCp_2Cl$, as evidenced by detailed NMR analysis, and the product **18** (Scheme 10). Self-dimerization of **18** must be more favorable than cross-aggregation, as in **23** and **24**. Under the catalytic conditions, the $EtZrCp_2Cl$ thus generated is to react with Et_3Al as above. One additional noteworthy finding is that addition of one equivalent of $ClAlEt_2$ relative to zirconacyclopentene **19** in the presence of 5-decyne and Et_3Al induces a smooth catalytic cycle. The 1:1 reaction of **19** and $ClAlEt_2$ should convert catalytically inactive **19** into catalytically active **23**. What was missing in the catalytically inactive system (Scheme 7) was an active form of Cl, either Cl–Al or Cl–Zr bonded species, which can bring together Zr and Al, or more specifically Cp_2ZrEt which can serve as an acidic component and Et_3Al (but not $ClAlEt_2$) which can serve as an effective base without tightly plugging the empty coordination site on Zr. At present, it is not clear whether the critical carbozirconation step is dissociative, involving a genuine 14-electron zwitterion.[33] Some associative processes involving 16-electron species appear equally or even more plausible. This point, however, remains to be clarified.



Scheme 8. Relationship between the extent of D incorporation and reaction conditions in the reaction of 5-decyne with Et_3Al in the presence of 1 equiv Cl_2ZrCp_2 (R = *n*Bu).

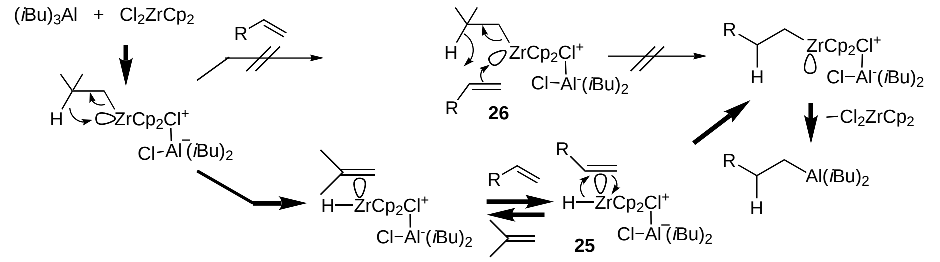


Scheme 9. Two independent syntheses of **20** as an active carbometalating agent, and a proposed mechanism for its formation.

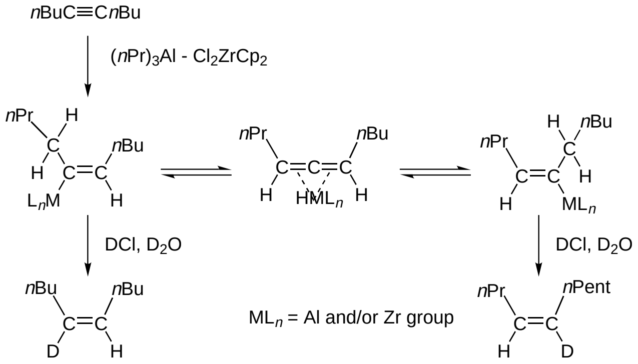


Scheme 10. Carbometalation of 5-decyne with **20**.

Hydrogen-transfer hydroalumination catalyzed by Zr and uncatalyzed or Al-catalyzed hydrozirconation: Attempts to carbometalate 5-decyne with $(n\mathrm{Pr})_3\mathrm{Al}$ in the presence of 10 mol% of $\mathrm{Cl_2ZrCp_2}$ in 1,2-dichloroethane led to hydroalumination in 87% yield along with only 9% of the expected *n*-propylalumination product. However, the hydroaluminated product was a mixture of the expected (*Z*)-5-decene (52% yield) and its regioisomer (*Z*)-4-decene (35% yield).[23] Careful examination did not detect any other regio- and stereoisomers. Regioisomerization involving only an adjacent position was initially puzzling, but it can be readily explained, if one assumes that the hydrometalated species, most probably an alkenylzirconium species, can undergo Lewis acid-assisted allene formation and that hydrometalation of allenes with the Al–Zr reagent strictly delivers H to the two terminal carbon atoms of the allene moiety. This interpretation is supported by the fact that only the fifth (but not the fourth) C of 4- and 5-decenes is deuterated upon treatment of the hydrometalated product with $\mathrm{DCl/D_2O}$ (Scheme 12). Since hydrozirconation of 5-decyne with Al-free $\mathrm{HZrCp_2Cl}$ regioselectively produces only (*Z*)-5-decene upon protonolysis,[34] the two processes are discrete. Involvement of an Al–Zr bimetallic activation is very likely in the $(n\mathrm{Pr})_3\mathrm{Al}$–$\mathrm{Cl_2ZrCp_2}$ reaction, even though it may be a synthetically undesirable process.



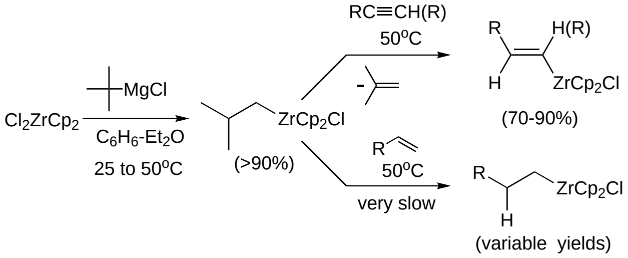
Scheme 13. Proposed mechanism for hydrogen-transfer hydroalumination of alkenes.



Scheme 12. Proposed mechanism for regioisomerization in the hydrogen-transfer hydrometalation of 5-decyne with $(n\mathrm{Pr})_3\mathrm{Al}$–$\mathrm{Cl_2ZrCp_2}$ and regioselective deuteration.

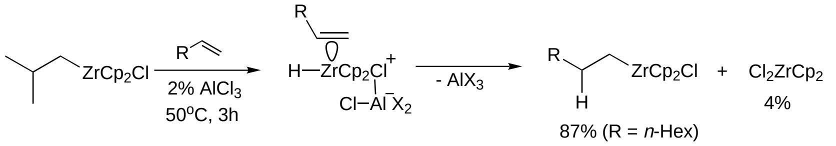
For Zr-catalyzed hydroalumination, $(i\mathrm{Bu})_3\mathrm{Al}$–$\mathrm{Cl_2ZrCp_2}$ is a synthetically more useful, superior reagent system, and it satisfactorily hydroaluminates various monosubstituted alkenes.[35] This work, published in 1980, appears to represent the first report on Zr-catalyzed hydrometalation. A mechanism involving the formation of $i\mathrm{BuZrCp_2Cl}$ by transmetalation and its H-transfer hydrozirconation of alkenes via a 6-membered transition state was initially proposed.[35] However, a recent study has shown that neither $(i\mathrm{Bu})_3\mathrm{Al}$ nor $i\mathrm{BuZrCp_2Cl}$ alone is capable of readily hydrometalating alkenes in high yields, strongly indicating that bimetallic activation must be required. The rate of the reaction of 1-alkenes with $(i\mathrm{Bu})_3\mathrm{Al}$ and $\mathrm{Cl_2ZrCp_2}$ (5 mol%) is independent of alkene concentration, which is consistent with the formation of a hydridozirconocene derivative, for example **25**, in the rate-determining step, but is not compatible with a direct six-centered process via **26** (Scheme 13). Interestingly, a reagent combination consisting of $(i\mathrm{Bu})_2\mathrm{AlH}$ and a catalytic amount (10 mol%) of $\mathrm{Cl_2ZrCp_2}$ is totally ineffective as a hydroaluminating agent under comparable conditions.[35]

Hydrozirconations of alkenes and alkynes are commonly carried out with preformed $\mathrm{HZrCp_2Cl}$,[34] which can be obtained as a pure reagent. However, its preparation is somewhat cumbersome, and various procedures for its in situ generation have been devised that use $\mathrm{LiAlH_4}$,[36, 37] $\mathrm{NaAlH_2(OCH_2CH_2OCH_3)_2}$,[35] $\mathrm{LiBH}(s\mathrm{Bu})_3$,[36, 38] and so on. However, one of the least expensive and cleanest is $i\mathrm{BuZrCp_2Cl}$, readily preparable in >90% yield by treating $\mathrm{Cl_2ZrCp_2}$ with 1–1.1 equiv of *t*BuMgCl.[36] The use of *i*BuMgCl in place of *t*BuMgCl gives plentiful $(i\mathrm{Bu})_2\mathrm{ZrCp_2}$. Hydrogen-transfer hydrozirconation of both terminal and internal alkynes with $i\mathrm{BuZrCp_2Cl}$ in benzene at 50 °C is a very satisfactory and convenient alternative to the hydrozirconation with pure $\mathrm{HZrCp_2Cl}$, and there are no complications caused by formation of two regioisomers (Scheme 14).[39]



Scheme 14. Synthetically useful hydrogen-transfer hydrozirconation of alkynes with $i\mathrm{BuZrCp_2Cl}$.

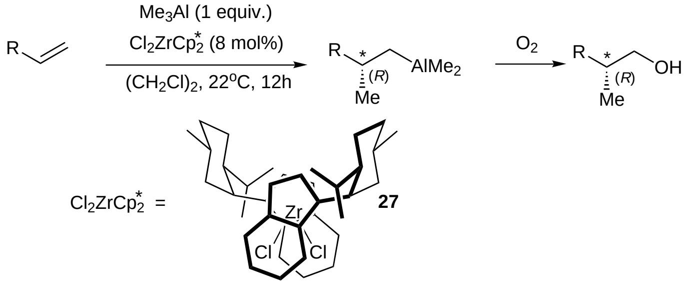
Unlike alkynes, however, alkenes have proved to be too unreactive to be practical in the hydrogen-transfer hydrozirconation with $i\mathrm{BuZrCp_2Cl}$, despite our earlier, more favorable claim.[36] We then reasoned that, if the Zr-catalyzed hydroalumination of alkenes with $(i\mathrm{Bu})_3\mathrm{Al}$ and $\mathrm{Cl_2ZrCp_2}$ should indeed proceed by Al-assisted hydrozirconation as shown in Scheme 13, it should also be feasible to achieve the stoichiometric hydrozirconation with a catalytic amount of an aluminum reagent using $i\mathrm{BuZrCp_2Cl}$ as a hydride source. This



Scheme 15. Aluminum-catalyzed hydrogen-transfer hydrozirconation of 1-alkenes (X = alkyl and/or Cl).

indeed proved to be the case, and a very practical procedure for hydrogen-transfer hydrozirconation of 1-alkenes with Cl_2ZrCp_2, *t*BuMgCl, and 2 mol% of $AlCl_3$ was developed[40] (Scheme 15).

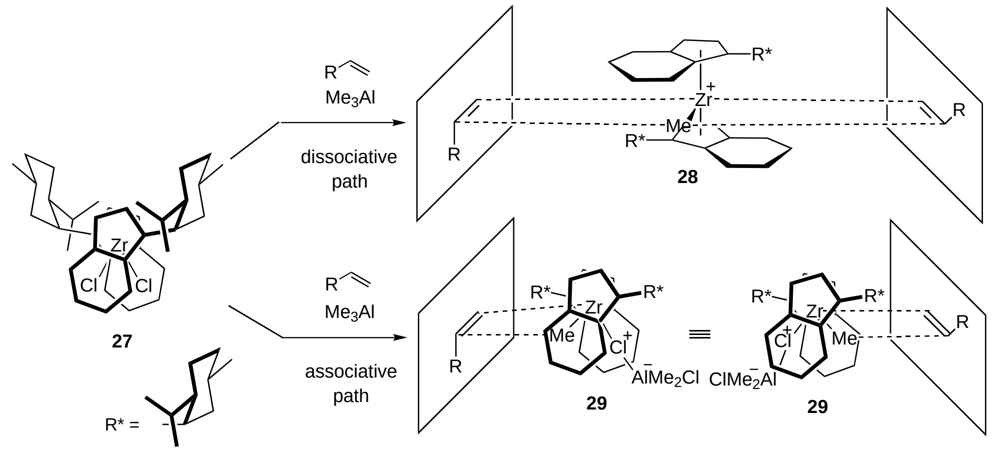
Zirconium-catalyzed enantioselective carboalumination of alkenes: If the Zr-catalyzed carboalumination reaction with alkenes occurs in a face-selective manner, an enantioselective conversion of alkenes to isoalkylaluminum derivatives would result. Attempts to apply the carboalumination reaction with Me_3Al in the presence of Cl_2ZrCp_2[20] to alkenes were initially all unsuccessful. In view of the facile Zr-catalyzed hydroalumination of alkenes with $(iBu)_3Al$ (Scheme 13),[35] even if isoalkylaluminum derivatives are produced by the desired carboalumination, they would be competitively consumed in the hydroalumination reaction shown in Scheme 13. This has indeed been recently confirmed.[41] The only high-yielding Zr-catalyzed carbometalation of alkenes known before 1990 or so was the Dzhemilev ethylmagnesation,[27] which proceeds by a cyclic mechanism (Scheme 5), and attempts to observe high *ee* values in this reaction have not been successful, the highest reported *ee* being 30–40%, except for some recent success with rather special allyl ethers and related heteroatom-substituted alkenes.[42, 43] Thus, the prospect for highly enantioselective Zr-catalyzed carbometalation of simple alkenes looked very bleak for many years. However, rationalism and generalization are, after all, human-generated dogmas, and they must be viewed with doubts and skepticism, especially when they pertain to some negative views. With this feeble optimism, we prepared and tested several chiral Cp derivatives, including some of those by Brintzinger[44] and Erker.[45] Contrary to the negative prospect presented above, the desired methylalumination of 1-alkenes with Me_3Al and $Cl_2ZrCp^*_2$, where Cp* is a chiral Cp derivative, proceeded in high yields (70–90%) in most cases.[41] Moreover, the use of Erker's C_2-symmetric Zr complex containing 1-neomenthylindene (**27**) led to a 65–75% *ee* to go along with the above-mentioned high chemical yields (Scheme 16 and Table 1). Initially, it was assumed that the formation of the monomethylated Zr-centered cationic intermediate (**28**) as an active transient species would be necessary to maintain C_2 symmetry.



Scheme 16. Zirconium-catalyzed enantioselective carboalumination of 1-alkenes with Me_3Al.

However, it has since been noted that the two Cl atoms in **27** are neither diastereotopic nor enantiotopic, but they are equivalent. Thus, replacement of either one with a Me group will produce identical species **29** of C_1 symmetry, which may then undergo either dissociative or associative *re*-face selective methylzirconation via **28** or **29**, respectively (Scheme 17). Although the formation of **28** induced by $ClAlMe_2$ must be viewed with skepticism, this point remains to be clarified.

As might be expected, the reaction of 1-decene with Et_3Al and **27** in nonpolar solvents like hexanes was clean but cyclic. After oxidation, 2-(*n*-octyl)-1,4-butanediol was obtained in 65% yield and only 33% *ee*.[46] Although the reaction of 1-decene with Et_2AlCl and **27** in 1,2-dichloroethane did not proceed well, the reaction of 1-hexene with Et_3Al and **27** (8 mol%) in 1,2-dichloroethane at 25 °C gave the expected



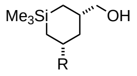
Scheme 17. Proposed mechanisms for zirconium-catalyzed enantioselective methylalumination of 1-alkenes with Me_3Al.

(*R*)-2-ethyl-1-hexanol in 65% yield with 68% *ee*. Since ethylalumination was faster than methylalumination, the reaction was run at 0 °C in most cases. After optimization with respect to solvents, 1,1-dichloroethane, along with 1,2-dichloroethane and dichloromethane, was found to be satisfactory. The chemical yields of ethylalumination were roughly 10–15% lower than those of methylalumination mainly due to somewhat more competitive hydroalumination, but the *ee* values observed with Et_3Al under optimized conditions were mostly >90%.[46] The observed dramatic switch in the course of reaction as the solvent was changed from hexanes to dichlorinated hydrocarbons is quite remarkable and very fortunate. The results of enantioselective ethylalumination are also summarized in Table 1.

Table 1. Zirconium-catalyzed enantioselective alkylalumination–oxidation to convert 1-alkenes to 2-alkyl-substituted 1-alkanols with trialkylalanes by means of **27** as a catalyst.[a]

Substrate	Me_3Al		Et_3Al	
	Yield [%]	% *ee*	Yield [%]	% *ee*
nBuCH=CH$_2$			74	93
nHexCH=CH$_2$	88	72		
nOctCH=CH$_2$			64	92
iBuCH=CH$_2$	92	74	77	90
PhCH$_2$CH=CH$_2$	77	70	69	93
cHexCH=CH$_2$	80	65	[b]	
tBuCH=CH$_2$	[b]		[b]	
HO(CH$_2$)$_4$CH=CH$_2$[c]	79	75	88[d]	90
Et$_2$N(CH$_2$)$_3$CH=CH$_2$[e]	68	71	56	95
Me$_2$Si(CH$_2$CH=CH$_2$)$_2$[f]	81	74	66	96

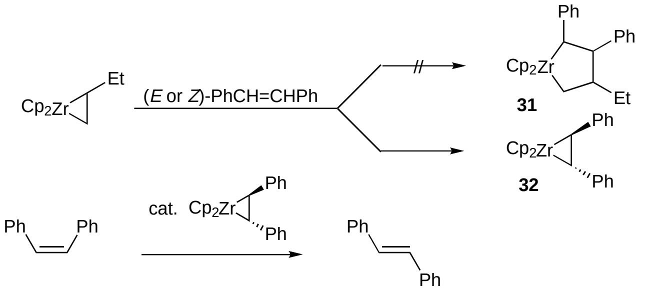
[a] The reactions were carried out using 8 mol% of **27** and Me_3Al or Et_3Al (1 equiv unless otherwise stated). Methylalumination was performed in 1,2-dichloroethane at 22 °C, while ethylalumination was performed in 1,1-dichloromethane at 0 °C unless otherwise indicated. After oxidation with O_2, (*R*)-2-alkyl-1-alkanols were obtained, unless otherwise noted. [b] No reaction observed. [c] Threefold excess of Me_3Al or Et_3Al was used, and the reaction with Et_3Al was carried out at 10 °C. [d] The alkylalane product was quenched with HCl. [e] Twofold excess of Me_3Al or Et_3Al was used, and the reaction with Et_3Al was carried out at 25 °C. [f] The initial alkylalumination products cyclized to give **30**, after oxidation.

30 =


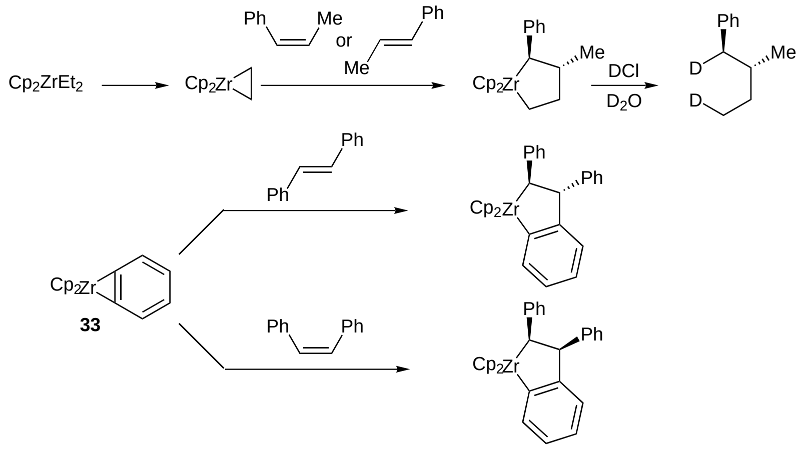
(R = Me or Et)

Zirconium-catalyzed stereoisomerization of alkenes: All examples of activation of electrophiles by electrophiles discussed so far deal with heterobimetallic dimeric association between Al and Ti or Zr, some of which were even planned on the basis of a rationally developed notion shown in Figure 1. On the other hand, the results discussed below were totally unexpected and novel. Although they may appear highly exotic, they seem to point to a widely observable strong intrinsic tendency for electrophiles to dimerize, or even polymerize in some cases, to boost their electrophilicity along the line of the principle shown in Figure 1.

During the course of a systematic investigation of the reactions of three-membered zirconacycles, such as zirconacyclopropanes and zirconacyclopropenes, with alkenes, alkynes, and related π-bonded compounds,[47] some unexpected results were obtained in the reaction of (1-butene)zirconocene generated from $(n\mathrm{Bu})_2ZrCp_2$ and (*E*)- and (*Z*)-stilbene. While none of the expected ring expansion reactions to give zirconacyclopentanes, such as **31**, took place, (*E*)-stilbenezirconocene was obtained in high yield in a stereoconvergent manner. It was soon found that (*Z*)-stilbene can be readily isomerized to the (*E*)-isomer by a catalytic amount of (*E*)-stilbenezirconocene (**32**).[48] In the absence of **32** no isomerization was detected (Scheme 18). Even in the ring expansion reaction of ethylenezirconocene with *β*-methylstyrene, complete *cis*-to-*trans* isomerization was observed.[49] This ring-expansion reaction accompanied by stereoisomerization should be contrasted with the stereospecific ring-expansion reaction of benzynezirconocene (**33**).[50] From the results presented above we may generalize that certain alkenezirconocenes undergo nonconcerted reactions with π-bonded compounds, whereas benzynezirconocenes and possibly other alkynezirconocenes are less prone to undergo such nonconcerted processes and tend to remain within the confines of concerted processes (Scheme 19). All these results shown in



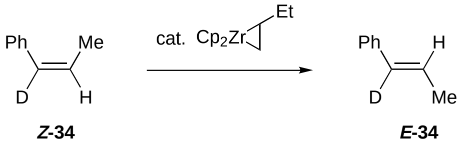
Scheme 18. Some nonconcerted stereoisomerizations of alkenes induced by alkenezirconocenes.



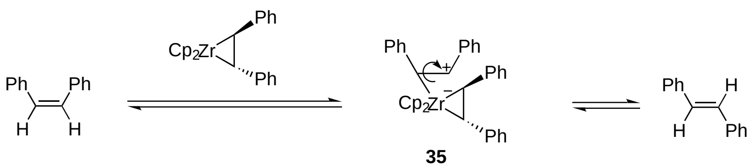
Scheme 19. Stereospecific vs. nonstereospecific conversions of three-membered into five-membered zirconacycles.

Schemes 18 and 19 presented an interesting puzzle as to how zirconocene derivatives might induce stereoisomerization.

Stereoisomerization of stereo- and regiodefined alkene (***Z***)**-34** is clean, and only its *E* isomer ((***E***)**-34**) is obtained without indications of the formation of other possible regioisomers and so on arising from skeletal rearrangements and other intermolecular processes.[49] So, it most probably involves simple cleavage, heterolytic or homolytic, of the π bond, accompanied by rotation and π-bond regeneration (Scheme 20). A study with several *p,p'*-disubstituted (*Z*)-stilbenes including stilbene itself clearly suggests heterolysis developing a positive charge on the benzylic carbon atom β to Zr.[49] These results pointed to a very reasonable heterolytic mechanism involving **35** (Scheme 21).

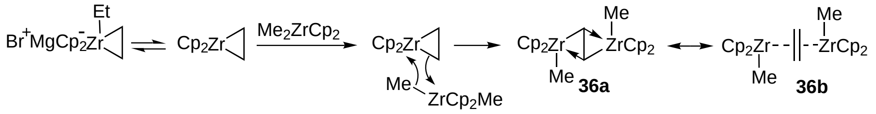


Scheme 20. Zirconium-catalyzed stereoisomerization of **34**, unaccompanied by rearrangements or other processes.



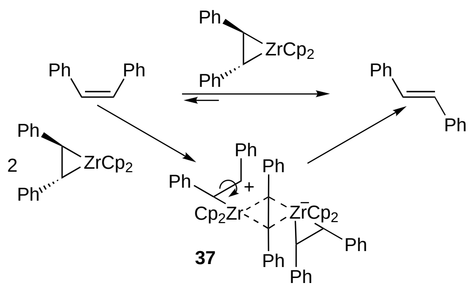
Scheme 21. Mechanism proposed initially for stereoisomerization of stilbenes.

However, a detailed kinetic study has revealed that the rate of isomerization is first-order in stilbene but second-order in the catalyst complex. This proved to be a major puzzle until a dimeric crystalline compound unexpectedly obtained from Me_2ZrCp_2 and ethylenezirconocene was shown by X-ray structure analysis to be a Cp_2ZrMe dimer with an inserted η^2-ethylene **36** (Scheme 22).[51]



Scheme 22. Formation of **36** from Me_2ZrCp_2 and ethylenezirconocene.

The proposed revised mechanism incorporates an η^2-stilbene-bridged dimeric complex shown in the proposed transient species **37**[49] (Scheme 23). One may ask why such a strange mode of dimerization might be involved. If one accepts the principle of activation of electrophiles through dimeric association, however, one should realize that it is a normal and expected course of event in cases where monomeric electrophiles are not sufficiently electrophilic.



Scheme 23. Revised mechanism for zirconium-catalyzed stereoisomerization of (*Z*)-stilbene.

How general is the principle of electrophile activation through dimeric association? Heterobimetallic activation in the Al/Ti and Al/Zr as well as many other bimetallic systems now appears to be an obvious and generally observable phenomenon for two electrophilic metallic species, and is detectable by various different kinds of facts and observations. Even in cases where the two interacting metals are the same, activation between two different species may be readily detected. For example, it has recently been observed that the Simmons–Smith reaction with $ClCH_2ZnCl$ can be dramatically accelerated by $ZnCl_2$.[52, 53] The results appear to be interpretable in terms of the principle proposed herein.[54]

On the other hand, electrophile activation through homodimerization is much less tangible and usually detectable only through kinetic studies showing often puzzling second-order kinetics with respect to electrophiles. If one looks at older literature on various acid-catalyzed reactions, such as addition of HCl to alkenes[55] and the Friedel–Crafts and related reactions,[56, 57] however, it is in fact difficult to avoid kinetic equations showing second-order dependence on acids. Furthermore, along with some untenable or unlikely termolecular mechanisms, one even finds suggestions for the involvement of dimeric acids, such as $H-Cl\cdots H-Cl$,[55] even though the principle of activation discussed here may not have been explicitly presented. In this connection, Olah's recent account[58] entitled Superelectrophiles is highly instructive, as it discusses the same electrophile activation principle, even though most of the superelectrophiles generated by protosolvation without the involvement of metals are de facto dications, which may exist only in superacidic media. In a limited number of cases, metallic homodimers, such as $Cl_2Al{-}Cl^+{-}Al^-Cl_3$ and $F_4Sb{-}F^+{-}Sb^-F_5$, are also discussed in the same context as that presented herein.

Conclusions

Electron-deficient metal compounds can be further activated as electrophiles through hetero- and homodimeric associative interactions as in **5**. In the extreme situation, even metal

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cations, such as **6**, may be generated. This simple principle of activation of electrophiles through dimeric association is fundamentally sound and appears to be unmistakable. It has in fact been widely encountered in many acid-catalyzed reactions including the Friedel–Crafts reaction and the Ziegler–Natta polymerization. And yet, its full recognition as a synthetically powerful principle does not appear to be widespread as yet. It may be further extended so as to include oligomeric and polymeric activations.

Several examples of heterobimetallic activation involving Al–Ti and Al–Zr systems observed mainly in the author's laboratories have been discussed here to illustrate the synthetic power of the principle. All but one of these examples involve bridging with halogens. In one case, a prototypical example involving activation through an η^2-alkene bridging is discussed. However, the effectiveness of bridging involving elements other than halogens, such as O, S, N, and H, must be further explored and scrutinized.

Singly bridged activated species, for example **5**, and their fully ionized limiting species, for example **6**, appear to fall into the category of superelectrophiles of Olah's definition.[58] Unlike protosolvated dicationic superelectrophiles and their monocationic bridged analogues, which may exist only in superacidic media, metal-centered superelectrophiles, especially those corresponding to **5**, are readily accessible, and they should even exist in ubiquitous dynamic monomer–dimer equilibria. Distinction between species represented by **5** and **6** is subtle, and may even be ignored in many cases. This must, however, be made through careful investigations involving kinetic, spectroscopic, and other measurements.

Correct recognition and full exploitation of the principle discussed herein will lead to the development of a variety of synthetically useful reactions catalyzed by metal electrophiles and to the observation of many more second-order kinetics with respect to both metallic and nonmetallic electrophiles.

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[1] a) H. C. Brown, *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, N.Y., **1972**; b) A. Pelter, K. Smith, H. C. Brown, *Borane Reagents*, Academic Press, New York, **1988.**

[2] a) J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA, **1987**; b) *Dictionary of Organometallic Compounds*, 2nd ed., Chapman & Hall, London, **1995**.

[3] H. C. Brown, *Hydroboration*, W. A. Benjamin, New York, **1962.**

[4] Some sterically highly congested dialkylboranes are monomeric: E. Negishi, J. J. Katz, H. C. Brown, *J. Am. Chem. Soc.* **1972**, *94*, 4025.

[5] T. Mole, E. J. Jeffery, *Organoaluminum Compounds*, Elsevier, Amsterdam, **1972.**

[6] *Comprehensive Organometallic Chemistry* (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1982.**

[7] For high-temperature hydroboration of ethylene with B_2H_6, see: D. T. Hurd, *J. Am. Chem. Soc.* **1948**, *70*, 2053.

[8] K. K. Wang, H. C. Brown, *J. Am. Chem. Soc.* **1982**, *104*, 7148.

[9] a) H. C. Brown, E. Negishi, *Pure Appl. Chem.* **1972**, *29*, 527; b) R. Köster, *Angew. Chem.* **1960**, *72*, 626; c) G. Zweifel, K. Nagase, H. C. Brown, *J. Am. Chem. Soc.* **1962**, *84*, 183, 190.

[10] H. C. Brown, E. Negishi, *J. Am. Chem. Soc.* **1972**, *29*, 527.

[11] E. Negishi, *Pure Appl. Chem.* **1981**, *53*, 2333.

[12] J. Boor, *Ziegler–Natta Catalysts and Polymerization*, Academic Press, New York, **1978**.

[13] H. Sinn, W. Kaminsky, *Adv. Organomet. Chem.* **1980**, *18*, 99.

[14] a) D. E. Van Horn, L. F. Valente, M. J. Idacavage, E. Negishi, *J. Organomet. Chem.* **1978**, *156*, C20; b) E. Negishi, D. Choueiry, In *Encyclopedia of Reagents for Organic Synthesis*, *Vol. 7* (Ed.: L. A. Paquette), Wiley, New York, **1995**, p. 5190.

[15] E. Negishi, D. Y. Kondakov, D. E. Van Horn, *Organometallics* **1997**, *16*, 951.

[16] a) F. N. Tebbe, G. W. Parshall, G. S. Reddy, *J. Am. Chem. Soc.* **1978**, *100*, 3611; b) F. N. Tebbe, R. L. Harslow, *J. Am. Chem. Soc.* **1980**, *102*, 6149.

[17] K. C. Ott, E. J. M. de Boer, R. H. Grubbs, *Organometallics* **1984**, *3*, 223.

[18] a) U. M. Dzhemilev, A. G. Ibragimov, O. S. Vostrikova, G. A. Tolstikov, L. M. Zelenova, *Izv. Akad. Nauk SSSR Ser. Khim.* **1981**, 361; b) U. M. Dzhemilev, A. G. Ibragimov, O. S. Vostrikova, G. A. Tolstikov, *Izv. Akad. Nauk SSSR Ser. Khim.* **1985**, 207.

[19] a) E. Negishi, M. J. Jensen, D. Y. Kondakov, S. Wang, *J. Am. Chem. Soc.* **1994**, *116*, 8404; b) D. Y. Kondakov, S. Wang, E. Negishi, *Tetrahedron Lett.* **1996**, *37*, 3803.

[20] a) D. E. Van Horn, E. Negishi, *J. Am. Chem. Soc.* **1978**, *100*, 2252; b) C. L. Rand, D. E. Van Horn, M. W. Moore, E. Negishi, *J. Org. Chem.* **1981**, *46*, 4093; c) E. Negishi, D. E. Van Horn, T. Yoshida, *J. Am. Chem. Soc.* **1985**, *107*, 6639.

[21] E. Negishi, T. Yoshinda, *J. Am. Chem. Soc.* **1981**, *103*, 4985.

[22] T. Yoshida, E. Negishi, *J. Am. Chem. Soc.* **1981**, *103*, 1276.

[23] E. Negishi, D. Y. Kondakov, D. Choueiry, K. Kasai, T. Takahashi, *J. Am. Chem. Soc.* **1996**, *118*, 9577.

[24] J. A. Miller, E. Negishi, *Tetrahedron Lett.* **1984**, *25*, 5863.

[25] E. Negishi, D. E. Van Horn, T. Yoshida, C. L. Rand, *Organometallics* **1983**, *2*, 563.

[26] E. Negishi, J. A. Miller, *J. Am. Chem. Soc.* **1983**, *105*, 6761.

[27] U. M. Dzhemilev, O. S. Vostrikova, R. M. Sultanov, *Izv. Akad. Nauk SSSR Ser. Khim.* **1983**, 213.

[28] T. Takahashi, T. Seki, Y. Nitto, M. Saburi, C. J. Rousset, E. Negishi, *J. Am. Chem. Soc.* **1991**, *113*, 6266.

[29] a) A. H. Hoveyda, Z. Xu, *J. Am. Chem. Soc.* **1991**, *113*, 5079; b) K. S. Knight, R. M. Waymouth, *J. Am. Chem. Soc.* **1991**, *113*, 6268.

[30] T. Takahashi, M. Kageyama, V. Denisov, R. Hara, E. Negishi, *Tetrahedron Lett.* **1993**, *34*, 687.

[31] a) H. Sinn, G. Oppermann, *Angew. Chem.* **1966**, *78*, 983; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 962; b) H. Sinn, E. Kolk, *J. Organomet. Chem.* **1966**, *6*, 373.

[32] a) W. Kaminsky, H. Sinn, *Liebigs Ann. Chem.* **1975**, 424; b) W. Kaminsky, H. J. Vollmer, *Liebigs Ann. Chem.* **1975**, 438; c) W. Kaminsky, J. Kopf, H. Sinn, H. J. Vollmer, *Angew. Chem.* **1976**, *88*, 688; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 629.

[33] a) G. Erker, R. Noe, D. Wingbermühle, *Chem. Ber.* **1994**, *127*, 805; b) for a review containing additional pertinent references, see: W. E. Piers, *Chem. Eur. J.* **1998**, *4*, 13.

[34] J. Schwartz, J. A. Labinger, *Angew. Chem.* **1976**, *88*, 402; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 333.

[35] E. Negishi, T. Yoshida, *Tetrahedron Lett.* **1980**, 1501.

[36] E. Negishi, J. A. Miller, T. Yoshida, *Tetrahedron Lett.* **1984**, *25*, 3407.

[37] S. L. Buchwald, S. J. LaMadre, R. B. Nielson, B. T. Watson, S. M. King, *Tetrahedron Lett.* **1987**, *28*, 3895.

[38] B. H. Lipshutz, R. Keil, E. L. Ellsworth, *Tetrahedron Lett.* **1990**, *31*, 7257.

[39] D. R. Swanson, T. Nguyen, Y. Noda, E. Negishi, *J. Org. Chem.* **1991**, *56*, 2590.

[40] H. Makabe, E. Negishi, unpublished results.

[41] D. Y. Kondakov, E. Negishi, *J. Am. Chem. Soc.* **1995**, *117*, 10771.

[42] a) J. P. Morken, M. T. Didiuk, A. H. Hoveyda, *J. Am. Chem. Soc.* **1993**, *115*, 6997; b) M. T. Didiuk, C. W. Johannes, J. P. Morken, A. H. Hoveyda, *J. Am. Chem. Soc.* **1995**, *117*, 7097.

[43] L. Bell, R. J. Whitby, R. V. H. Jones, M. C. H. Standen, *Tetrahedron Lett.* **1996**, *37*, 7139.

[44] a) F. R. W. P. Wild, L. Zsolnai, G. Huttner, H. H. Brintzinger, *J. Organomet. Chem.* **1982**, *232*, 233; b) R. R. W. P. Wild, M. Wasiucionek, G. Huttner, H. H. Brintzinger, *J. Organomet. Chem.* **1985**, *288*, 63.

[45] G. Erker, M. Aulbach, M. Knickmeier, D. Wingbermuhle, C. Kruger, M. Nolte, S. Werner, *J. Am. Chem. Soc.* **1993**, *115*, 4590.

[46] D. Y. Kondakov, E. Negishi, *J. Am. Chem. Soc.* **1996**, *118*, 1577.

[47] a) E. Negishi, T. Takahashi, *Synthesis* **1988**, 1; b) E. Negishi in *Comprehensive Organic Synthesis*, *Vol. 5* (Ed.: L. A. Paquette), Pergamon, Oxford, **1991**, 1163; c) E. Negishi, T. Takahashi, *Acc. Chem. Res.* **1994**, *27*, 124.

[48] T. Takahashi, D. R. Swanson, E. Negishi, *Chem. Lett.* **1987**, 623.

[49] E. Negishi, D. Choueiry, T. B. Nguyen, D. R. Swanson, N. Suzuki, T. Takahashi, *J. Am. Chem. Soc.* **1994**, *116*, 9751.

[50] K. Kropp, G. Erker, *Organometallics* **1982**, *1*, 1246.

[51] T. Takahashi, K. Kasai, N. Suzuki, K. Nakajima, E. Negishi, *Organometallics*, **1994**, *13*, 3413.

[52] E. C. Friedrich, S. E. Lunetta, E. J. Lewis, *J. Org. Chem.* **1989**, *54*, 2388.

[53] A. B. Charette, H. Juteau, *J. Am. Chem. Soc.* **1994**, *116*, 2651.

[54] E. Nakamura, A. Hirai, M. Nakamura, *J. Am. Chem. Soc.* **1998**, *120*, 5844. The author thanks Prof. E. Nakamura for the disclosure of his unpublished results.

[55] a) Y. Pocker, K. D. Stevens, J. J. Champoux, *J. Am. Chem. Soc.* **1969**, *91*, 4199; b) Y. Pocker, K. D. Stevens, *J. Am. Chem. Soc.* **1969**, *91*, 4205.

[56] a) G. A. Olah, *Friedel–Crafts and Related Reactions*, Interscience, New York, **1963**; b) R. M. Roberts, A. A. Khalaf, *Friedel–Crafts Alkylation Chemistry*, Marcel Dekker, New York, **1984.**

[57] a) F. P. DeHaan, H. C. Brown, *J. Am. Chem. Soc.* **1969**, *91*, 4844; b) B. J. Carter, W. D. Covey, F. P. DeHaan, *J. Am. Chem. Soc.* **1975**, *97*, 4783.

[58] G. A. Olah, *Angew. Chem. Int. Ed. Engl.* **1993**, *105*, 805; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 767.

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