

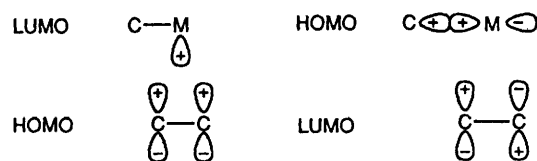
# An Odyssey from Stoichiometric Carbotitanation of Alkynes to Zirconium-catalysed Enantioselective Carboalumination of Alkenes

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## 1 Introduction

Until recently, the use of organometals in organic synthesis had been dominated by polar reactions of organometals, such as organolithiums and Grignard reagents, with polar electrophiles, such as alkyl halides, ketones and other carbonyl compounds, as well as nitriles.<sup>1</sup> Although carbon–carbon bond formation *via* organometallic reactions of nonpolar compounds, such as oligomerization and polymerization of alkenes, alkynes and dienes, has been known for several decades, most of the early examples were limited to the synthesis of highly symmetrical molecules, such as benzene, cyclododecatriene and polyethylene.<sup>2</sup> As such, these reactions and procedures were not readily applicable to the synthesis of complex organic molecules of low symmetry. Nonetheless, addition of carbon–metal bonds to alkenes and alkynes, termed *carbometallation*,<sup>3</sup> may, in principle, be achieved in a controlled manner so that it would be applicable to the synthesis of unsymmetrical molecules. Carbometallations may proceed by various mechanisms, but those proceeding *via* pericyclic reactions are of particular interest to us, because they can be facile and highly stereoselective. For the crucial step of such processes, a four-centred *syn* addition mechanism represented by Scheme 1 may be proposed. If this mechanism indeed operates, the crucial structural requirement for organometallic reagents is the presence or ready



Scheme 1

Ei-ichi Negishi received the bachelor's degree from the University of Tokyo in 1958. While he was a research chemist at Teijin, Ltd, Japan, he came to the University of Pennsylvania as a Fulbright Scholar in 1960 and received his PhD degree in 1963. He joined Professor H. C. Brown's research group at Purdue University as a postdoctoral associate in 1966 and became his assistant in 1968. In 1972 he moved to Syracuse University as Assistant Professor and was promoted to Associate Professor in 1976. He returned to

Purdue University as Professor in 1979. He is the author of about 250 scientific publications. His recent work has centred on the use of transition-metal complexes as catalytic reagents in organic synthesis. Some transition metal-catalysed reactions developed by him and his students include Pd- or Ni-catalysed cross-coupling, Pd-catalysed cyclic carbopalladation reactions, and Zr- or Ti-catalysed carbometallation reactions.



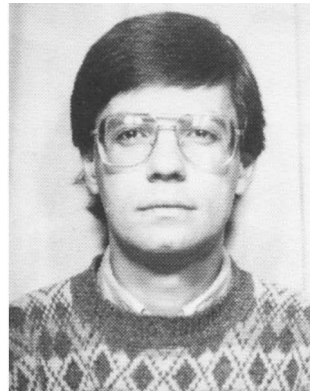
availability of a low-lying metal empty orbital. Since one can write essentially the same mechanism for hydrometallation by merely replacing C with H, we reasoned that those metals which readily participate in hydrometallation, such as B, Al and Zr, should also participate in carbometallation but that the activation energy for carbometallation would be generally higher than that for the corresponding hydrometallation reaction due to the greater steric requirements of C groups relative to H and more highly directionalized sp<sup>2</sup>-hybridized C orbitals as compared with the non-directional s orbital of H. We further reasoned that one way of promoting such carbometallation processes might be to resort to *dynamic polarization* between two Lewis acids (or electrophiles) which makes one of them more acidic (or electrophilic), while making the other more basic (or nucleophilic). As generally accepted, this might indeed be the mode of activation in a wide variety of Lewis acid-catalysed reactions, such as the Ziegler–Natta polymerization<sup>4</sup> and the Friedel–Crafts reaction.<sup>5</sup> As discussed by us some 15 years ago,<sup>3b</sup> interactions between two metal-containing Lewis acids 'M'L and 'M<sup>2</sup>L can lead to (i) 'ate' complexation, (ii) dynamic polarization and (iii) transmetalation among others (Scheme 2), and some of these processes can serve as crucial steps in catalytic cycles. With these simplistic notions in mind, we embarked on a long-range investigation of developing carbometallation reactions of B, Al, Zr and other metals promoted or catalysed by Lewis acids, such as those containing B, Al, Ti, Zr and other metals.

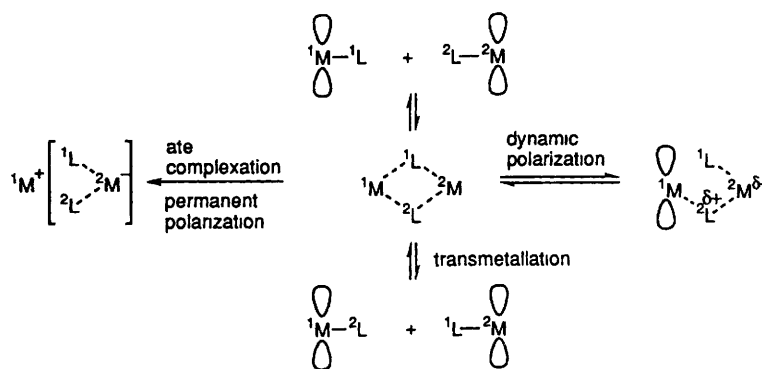
## 2 Stoichiometric Carbotitanation of Alkynes vs. Formation of Tebbe Reagent and its Reaction with Alkynes

With the development of regio- and stereo-selective methods for converting alkynes into tri- and tetra-substituted alkenyl derivatives as one of the major goals, the reaction of alkynes with Al–Ti reagents was considered. Treatment of terminal alkynes with organoalanes was known to give mainly alkynylalanes *via* terminal H abstraction, and the same reaction of internal alkynes was known to require rather drastic conditions leading to the formation of oligomeric products.<sup>6</sup> In sharp contrast, the reaction of diphenylacetylene with 2 equiv. of Me<sub>3</sub>Al and 1 equiv. of Cp<sub>2</sub>TiCl<sub>2</sub>, where Cp is η<sup>5</sup>-cyclopentadienyl, was complete within 12 h at 20–22 °C to give,

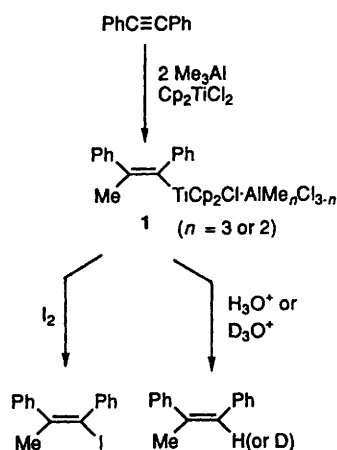
Denis Y. Kondakov was born in St. Petersburg, Russia, in 1965. He received his MS (1987) and PhD (1991) degrees from St. Petersburg University, Russia, where he worked with Professor Alexey

Dneprovskii. He was then awarded a JSPS postdoctoral fellowship and joined the group of Professor Tamotsu Takahashi at IMS, Okazaki, Japan. He is currently a postdoctoral research associate with Professor Ei-ichi Negishi at Purdue University. His research interests are mainly in the development of new and synthetically attractive reactions mediated by organotransition metal compounds.

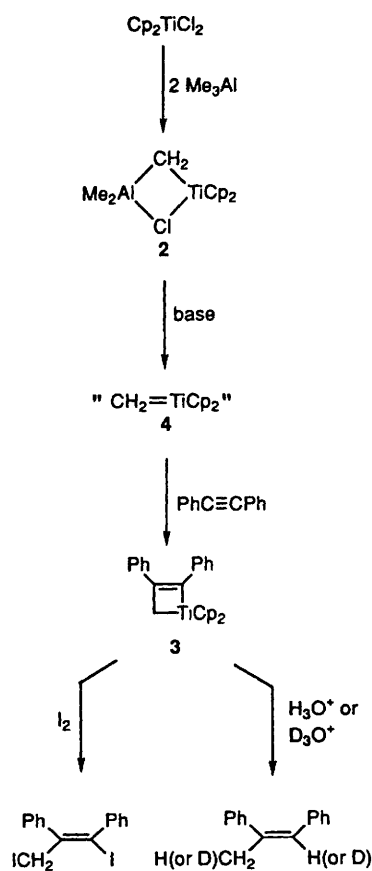




Scheme 2



Scheme 3



Scheme 4

upon hydrolysis, >98% (*Z*)- $\alpha$ -methylstilbene in 84% yield, while iodinolysis gave (*E*)- $\alpha$ -iodostilbene in 75% yield.<sup>7</sup> Although the detailed structure of the organometallic product was not established in the original study, it has recently been identified as an alkenyltitanium complex **1**<sup>8</sup> (Scheme 3). As might be expected on this basis, the reaction is only stoichiometric in Ti, and our brief attempts to develop its catalytic version have not so far been successful.

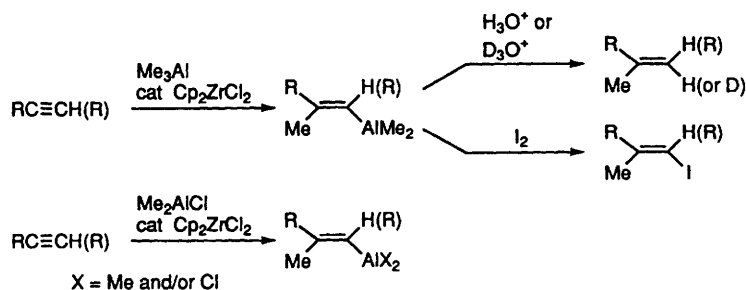
In a concurrent and independent study, Tebbe<sup>9</sup> reported that the reaction of  $\text{Me}_3\text{Al}$  and  $\text{Cp}_2\text{TiCl}_2$  in the same 2 : 1 ratio would produce a bimetallic complex **2**, known as the Tebbe reagent, the formation of which must involve  $\alpha$ -C–H activation as elucidated by Grubbs<sup>10</sup> (Scheme 4). Interestingly, the reaction of **2** with  $\text{PhC}\equiv\text{CPh}$  was shown a year later to give a titanacyclobutene **3** presumably via carbometallation of methylenetitanocene (**4**) with  $\text{PhC}\equiv\text{CPh}$ .<sup>11</sup> Thus, the same reagent combination, *i.e.*  $\text{Me}_3\text{Al}$ ,  $\text{Cp}_2\text{TiCl}_2$  and  $\text{PhC}\equiv\text{CPh}$ , in the same molar ratio but mixed in different sequences and time intervals has led to two discrete processes. These early results were already pointing to the intriguingly multi-faceted nature of carbometallation reactions of early transition metal–Al reagents.

### 3 Zirconium-catalysed Carboalumination of Alkynes

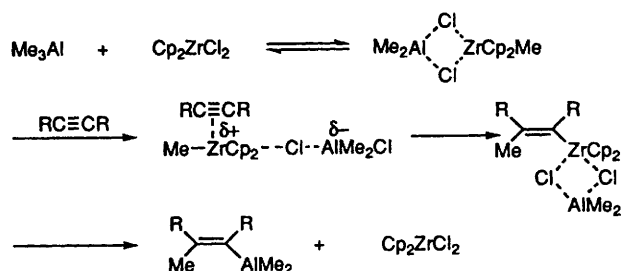
#### 3.1 Methylalumination of Alkynes

Although interesting, the carbometallation reaction of alkynes<sup>7</sup> turned out to be of limited synthetic scope, besides being only stoichiometric in Ti. In a situation of this nature, it is often profitable to screen other metals of the same triad and of the neighbouring groups. Indeed, we discovered that the use of  $\text{Cp}_2\text{ZrCl}_2$  in place of  $\text{Cp}_2\text{TiCl}_2$  led to a similar but catalytic reaction of much greater synthetic value shown in Scheme 5.<sup>3a, 12</sup> This reaction is, in principle, competitive with Normant's carbocupration,<sup>2, 13</sup> but the two reactions have turned out to be synthetically rather complementary to each other. Specifically, the Zr-catalysed carboalumination reaction can readily handle the cases of carbometallation with methyl,<sup>3a, 12</sup> allyl<sup>14</sup> and benzyl<sup>14</sup> groups. These groups do not appear to be readily accommodated by carbocupration. The Zr-catalysed carboalumination reaction is relatively unaffected by proximal heteroatoms such as halogens, O, S,<sup>15a</sup> and Si,<sup>15b</sup> permitting the synthesis of trisubstituted alkenes containing two heterofunctional groups which can be used to synthesize a wide variety of terpenoids and carotenoids. On the other hand, proximal heteroatoms significantly affect the regio- and stereo-chemistry of carbocupration. As of 1994, the syntheses of over 40 simple and complex natural products have made use of the Zr-catalysed alkyne carboalumination reaction. No further discussion of the synthetic aspects of the reaction is permitted here, and our previous reviews<sup>3b, 16</sup> should be consulted for further details.

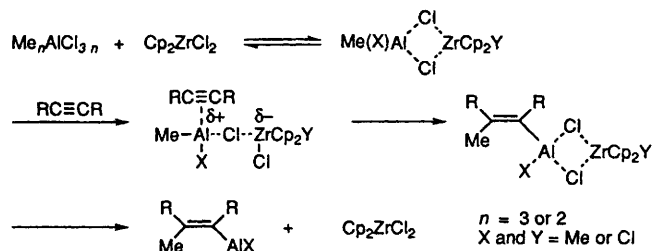
Clarification of the mechanism of the Zr-catalysed methylalumination has proved to be very challenging. We initially envisioned that the reaction might involve (i) methylation of  $\text{Cp}_2\text{ZrCl}_2$  with  $\text{Me}_3\text{Al}$  to produce  $\text{MeZrCp}_2\text{Cl}$  and  $\text{Me}_2\text{AlCl}$ , (ii) methylzirconation of alkynes to give alkenylzirconium derivatives, which most likely is promoted by an Al reagent, and (iii) their reverse transmetalation with  $\text{Me}_2\text{AlCl}$  to yield the observed alkenyldimethylalanes with regeneration of  $\text{Cp}_2\text{ZrCl}_2$  (Scheme 6).



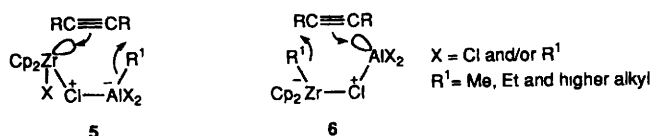
Scheme 5



Scheme 6



Scheme 7

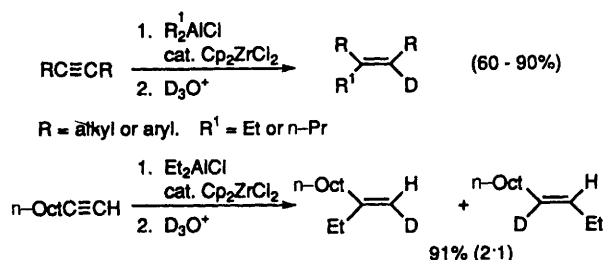


Scheme 8

This was supported by observation of a reversible Me–Cl exchange between  $\text{Me}_3\text{Al}$  and  $\text{Cp}_2\text{ZrCl}_2$  by NMR spectroscopy<sup>17</sup> and the stoichiometric reaction of  $\text{RC}\equiv\text{CAlMe}_2$  with preformed  $\text{MeZrCp}_2\text{Cl}$  among others (Scheme 5).<sup>18</sup> However, our subsequent study has indicated that it might actually involve direct addition of the Me–Al bond to alkynes promoted by a  $\text{ZrCp}_2$  derivative<sup>17</sup> (Scheme 7). Thus, for example,  $\text{Me}_2\text{AlCl}$ – $\text{Cp}_2\text{ZrCl}_2$  is a reasonable methylaluminating agent,<sup>17</sup> even though no Me–Cl exchange between the two compounds to produce  $\text{MeZrCp}_2\text{Cl}$  is detectable by NMR spectroscopy. In view of the Curtin–Hammett principle, however, rigorous exclusion of the mechanism shown in Scheme 6 cannot be made on the basis of the currently available data. Furthermore, other six-centred mechanisms, such as those represented by **5** and **6**, (Scheme 8) must also be given serious considerations. Regardless of the precise mechanisms, however, these Zr-catalysed methylalumination reactions must not involve  $\alpha$  C–H activation.

### 3.2 Alkylalumination of Alkynes *via* Simple Addition of Alkyl–Metal Bonds

The Zr-catalysed alkylalumination of alkynes with alkylalanes containing Et and higher alkyl groups initially proved to be problematic. However, it has been found that the reaction of alkynes with

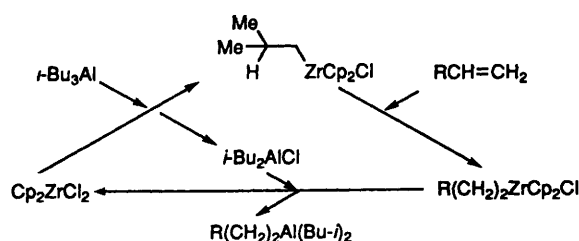


Scheme 9

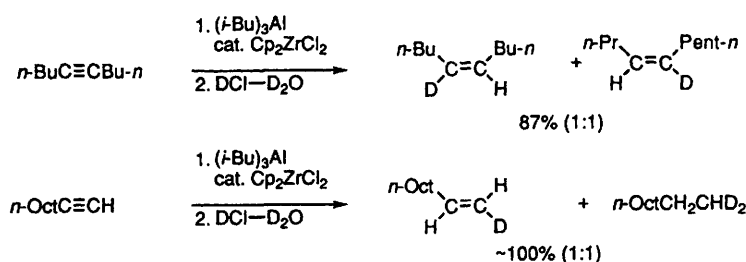
$\text{R}_2\text{AlCl}$ – $\text{Cp}_2\text{ZrCl}_2$  reagent systems rather than  $\text{R}_3\text{Al}$ – $\text{Cp}_2\text{ZrCl}_2$  combinations in chlorinated hydrocarbons, *e.g.*  $(\text{CH}_2\text{Cl})_2$ , can provide the desired *syn* alkylalumination products in good yields,<sup>12</sup> although its regioselectivity appears to be significantly lower than that of methylalumination (Scheme 9). Relatively little is known about the mechanism of these reactions, but several four- and six-centred processes similar to those considered for methylalumination may be considered. Here again, there is no indication of C–H activation. On the other hand, some related reactions of  $\text{Et}_3\text{Al}$  and  $\text{Pr}^i_3\text{Al}$  have turned out to represent a major mechanistic surprise, as discussed later.

## 4 Hydroalumination of Alkenes and Alkynes with Triisobutylalane and Zirconocene Dichloride

One significant limitation of the Zr-catalysed carboalumination is that isoalkylalanes, *e.g.*  $\text{Bu}^i_3\text{Al}$ , do not undergo carboalumination. Instead,  $\text{Bu}^i_3\text{Al}$ – $\text{Cp}_2\text{ZrCl}_2$  acts as a hydroaluminating agent. Both alkenes and alkynes<sup>19,20</sup> can be hydroaluminated. For the hydroalumination reaction of alkenes, a mechanism shown in Scheme 10 has been proposed.<sup>19</sup> Examination by NMR spectroscopy of some reaction mixtures indicates that the initial hydrozirconation products, *i.e.* chloroalkylzirconocenes, build up and subsequently decay, supporting the transmetalation–hydrozirconation–reverse transmetalation mechanism. The mechanism involving hydrozirconation with  $\text{Bu}^i\text{ZrCp}_2\text{Cl}$  has been further supported by the fact that  $\text{Bu}^i\text{ZrCp}_2\text{Cl}$  generated by the treatment of  $\text{Cp}_2\text{ZrCl}_2$  with  $\text{Bu}^i\text{MgCl}$  does hydrozirconate alkenes<sup>21</sup> and alkynes.<sup>22</sup> However, it is not clear at the present time whether  $\text{Bu}^i\text{ZrCp}_2\text{Cl}_2$  first undergoes dehydrozirconation to give  $\text{HZrCp}_2\text{Cl}$ , which then hydrozirconates alkenes and alkynes. An alternative possibility that  $\text{Bu}^i\text{ZrCp}_2\text{Cl}$  interacts directly with carbon–carbon  $\pi$  bonds *via* a six-centred



Scheme 10



Scheme 11

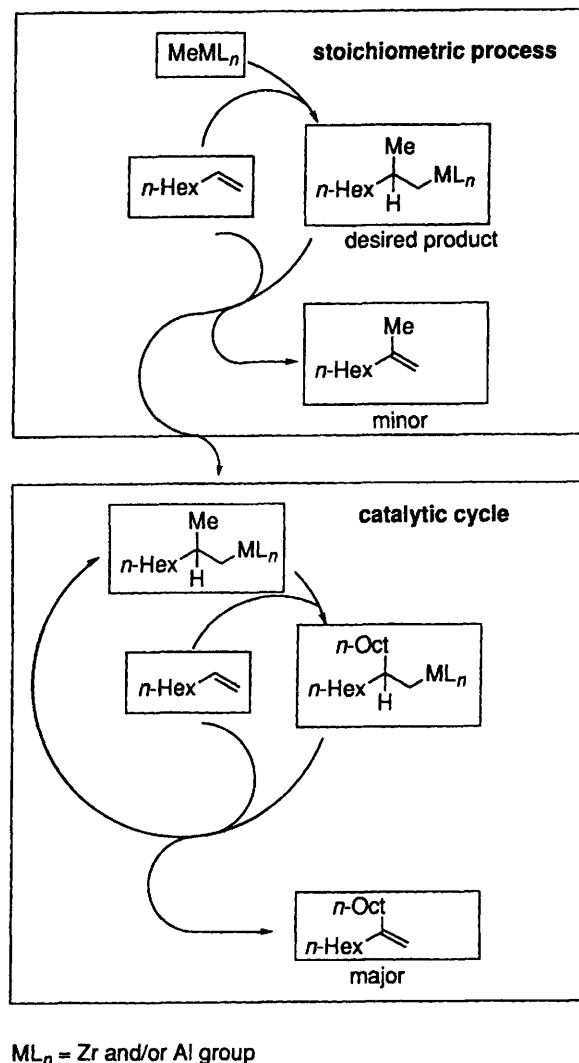
transition state must be considered seriously. Regardless of the precise mechanistic details, both  $\text{Bu}_3\text{Al}-\text{Cp}_2\text{ZrCl}_2$  and preformed  $\text{BuZrCp}_2\text{Cl}$  serve as convenient alternatives to  $\text{HZrCp}_2\text{Cl}$ . However, some significant differences between  $\text{HZrCp}_2\text{Cl}$  and  $\text{Bu}_3\text{Al}-\text{Cp}_2\text{ZrCl}_2$  have also been observed. For example, the reaction of dec-5-yne with  $\text{Bu}_3\text{Al}-\text{Cp}_2\text{ZrCl}_2$  gives, after deuteration, an essentially 1:1 mixture of (Z)-5-deuterio-dec-5-ene and (Z)-5-deuterio-dec-4-ene<sup>20</sup> and the corresponding reaction of dec-1-yne produces a mixture of (E)-1-deuterio-dec-1-ene and 1,1-dideuterio-decane<sup>20</sup> (Scheme 11). These results indicate that the synthetic scope and mechanistic details of the hydrozirconation processes involving the use of various 'HZrCp<sub>2</sub>Cl' equivalents may vary and must therefore be carefully examined and delineated.

## 5 Dzhemilev Ethylmagnesiumation of Alkenes and its Mechanism Involving Cyclic Carbozirconation *via* $\beta$ C-H Activation

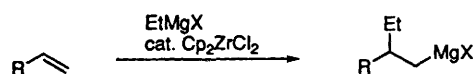
One of our earlier disappointments was that the reaction of  $\text{Me}_3\text{Al}-\text{Cp}_2\text{ZrCl}_2$  with alkenes, e.g. oct-1-ene, did not provide the desired methylalumination products. In retrospect, this failure was to be expected. Since the desired products are isoalkylalanes, they can undergo competitive hydroalumination of the starting alkenes discussed in the preceding section, unless the desired methylalumination reaction is considerably faster than the competing hydroalumination process. Our recent investigation has established that the reaction of oct-1-ene with  $\text{Me}_2\text{Al}-\text{Cp}_2\text{ZrCl}_2$  indeed gives 2-hexyl-oct-1-ene as the major product along with a smaller amount of 2-methyl-oct-1-ene,<sup>23</sup> both of which must have been formed *via* carbometallation-dehydrometallation as depicted in Scheme 12.

In view of the results with methylalanes described above, Dzhemilev's report on the Zr-catalysed ethylmagnesiumation of alkenes<sup>24</sup> (Scheme 13) came as a surprise to us. We were further intrigued by the fact that neither methylmagnesium nor higher alkylmagnesium derivatives<sup>25</sup> participated satisfactorily in this reaction, but we had little intention to pursue these puzzles, as our main interest in the organozirconium area had already been shifted to a seemingly unrelated topic of the chemistry of low oxidation state 'ZrCp<sub>2</sub>' derivatives.

Following the initial and promising discovery that enynes undergo 'ZrCp<sub>2</sub>'-promoted bicyclization leading to the formation of monocyclic and bicyclic organic compounds<sup>26</sup> (Scheme 14), we embarked on a systematic investigation on (i) the  $\beta$ -H abstraction reaction of dialkylzirconocene<sup>27</sup> to produce alkene zirconocenes or zirconacyclopentanes,<sup>28</sup> (ii) their ring expansion reactions with alkenes and alkynes *via* carbozirconation,<sup>29</sup> and (iii) various subsequent reactions of five-membered zirconacycles<sup>30</sup> (Scheme 15). A number of other workers have also contributed to this area, but the scope of this review does not permit a detailed presentation of their significant contributions. For further details of these processes, recent reviews by us<sup>31</sup> and others<sup>32</sup> as well as pertinent references therein should be consulted. In one specific example, we have found that treatment of  $\text{Cp}_2\text{ZrCl}_2$  with 2 equiv. of  $\text{EtMgBr}$  gives  $\text{Et}_2\text{ZrCp}_2$  which smoothly decomposed at or above 0 °C to produce (ethylene)zirconocene, which reacts with alk-1-enes to give 'pair'-selectively and regioselectively 3-alkyl-substituted zirconacyclopentanes in nearly quantitative yield.<sup>33</sup> When 3, rather than 2, equiv. of  $\text{EtMgBr}$  was accidentally employed, however, a totally different set of products consisting of a 2-ethylalkylmagnesium derivative and



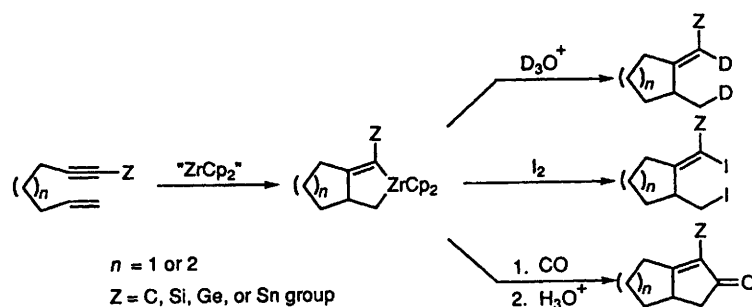
Scheme 12



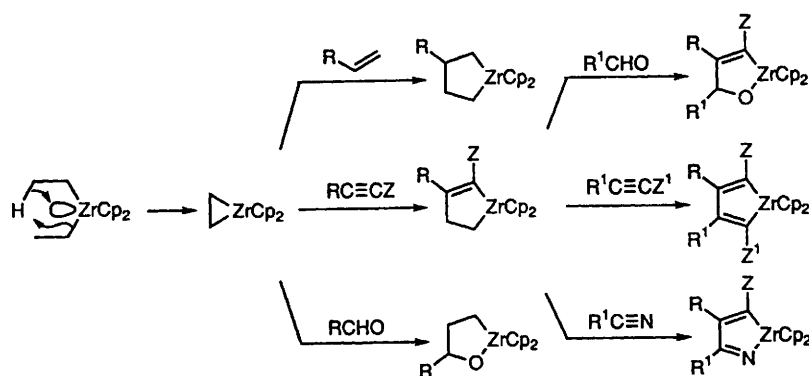
Scheme 13

(ethylene)zirconocene, which could be trapped as its  $\text{PMe}_3$  complex, was obtained.<sup>33</sup> Clearly, the third equivalent of  $\text{EtMgBr}$  reacted with the zirconacyclopentane derivative, and the course of the reaction has been clarified as shown in Scheme 16.<sup>33</sup> Perhaps more significantly, however, it one day dawned on us that a series of the three discrete *stoichiometric* reactions, one of which was a totally serendipitous discovery, would add up to Dzhemilev's Zr-catalysed ethylmagnesiumation of alkenes (Scheme 17). More suggestive and less detailed concurrent and subsequent studies by others<sup>34</sup>

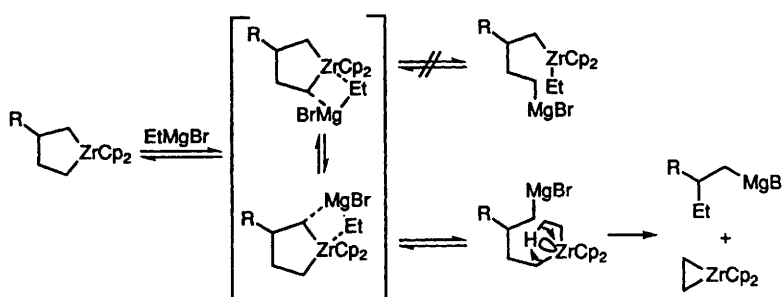




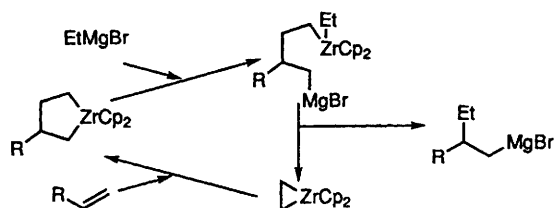
Scheme 14



Scheme 15



Scheme 16



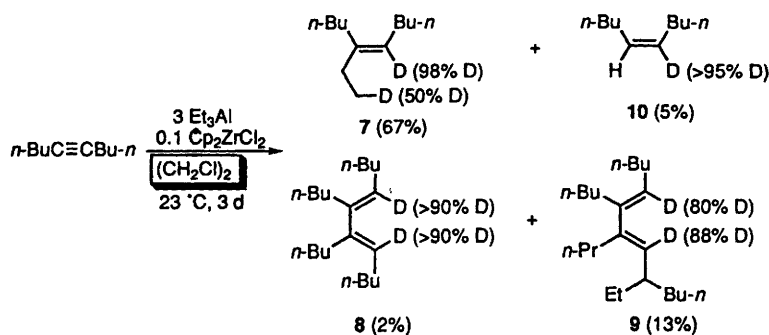
Scheme 17

have also revealed similar, but not necessarily the same, cyclic mechanisms. It is striking and instructive that the reaction which might have initially appeared to involve a straightforward addition of an ethyl-metal bond to an alkene actually involves such an intricate cyclization-ring opening process. Furthermore, these intriguing findings have sent us a clear and burdensome warning that, for any carbometallation reactions involving Zr or perhaps even other related transition metals, such as Ti and Hf, cyclic mechanisms *via* C–H activation must be considered along with the more straightforward addition processes.

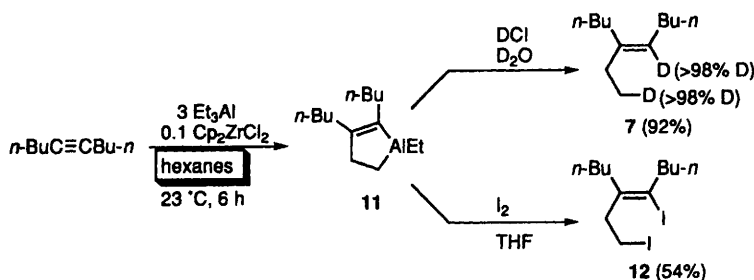
## 6 Zirconium-catalysed Cyclic Carboalumination of Alkynes *via* Bimetallic C–H Activation

As indicated in Section 3, the reaction of alkynes with trialkylalanes– $\text{Cp}_2\text{ZrCl}_2$  reagent systems in chlorinated hydro-

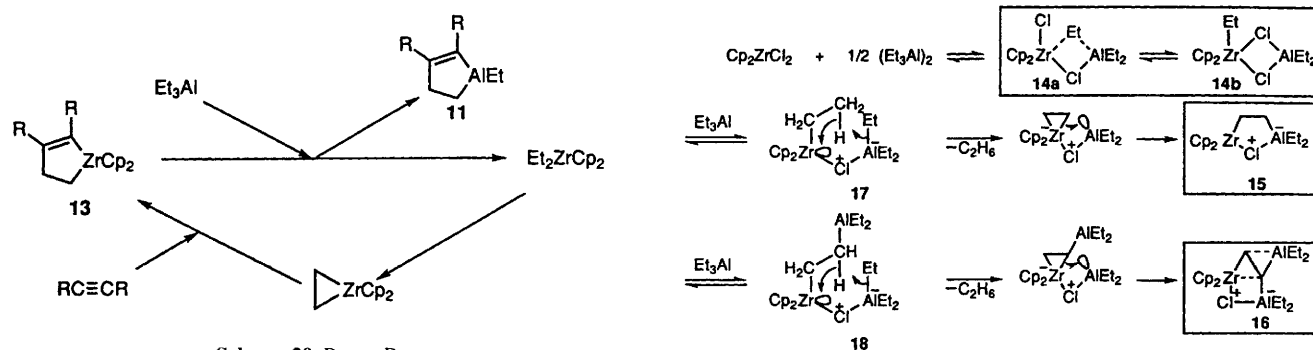
carbons, *e.g.*  $(\text{CH}_2\text{Cl})_2$ , proved to be rather complex, even though the corresponding reaction of  $\text{R}_2\text{AlCl}–\text{Cp}_2\text{ZrCl}_2$  was much cleaner and synthetically useful. Thus, for example, the reaction of dec-5-yne with  $\text{Et}_3\text{Al}$  (3 equiv.) and 10 mol% of  $\text{Cp}_2\text{ZrCl}_2$  in  $(\text{CH}_2\text{Cl})_2$  at 23 °C for 3 days produced, after deuteration, **7** as the major product along with a couple of alkyne dimers (**8** and **9**) and a hydroalumination product **10** formed as minor byproducts<sup>8</sup> (Scheme 18). Incorporation of two deuterium atoms in **7–9** was a strong indication that some cyclic carbometallation processes *via* C–H activation must have taken place. The fact that the Me group in the Et moiety of **7** was only 50% deuterated indicated that it must have been formed *via* partially cyclic and partially acyclic processes. This reaction was reported as early as 1978,<sup>3a,12,35</sup> but these intricate details had remained unnoticed until recently. In contrast with the reactions with methylalanes,  $\text{Et}_2\text{AlCl}$ , and  $\text{Pr}_2\text{AlCl}$ , proceeding readily in chlorinated hydrocarbons (*vide supra*), that with  $\text{Et}_3\text{Al}$  proceeded faster and more cleanly in non-polar solvents, *e.g.* hexanes, producing nearly exclusively a cyclic carboalumination product represented by **11**, which gave **7** and **12** upon deuteration and iodination, respectively (Scheme 19). In the light of the mechanism of the Dzhemilev ethylmagnesiumation discussed earlier, we initially assumed that this reaction too must proceed *via*  $\text{Et}_2\text{ZrCp}_2$  formed by double transmetalation reaction of  $\text{Et}_3\text{Al}$  and  $\text{Cp}_2\text{ZrCl}_2$  and (ethylene)zirconocene. The latter is known to undergo a ‘pair’-selective ring expansion reaction with alkynes to give the corresponding zirconacyclopentenes<sup>30b</sup> which



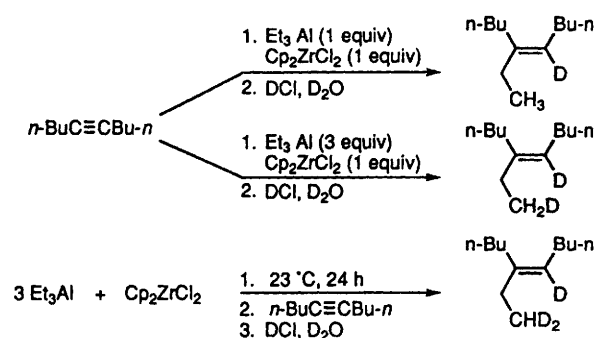
Scheme 18



Scheme 19

Scheme 20 R = *n*-Bu

Scheme 21

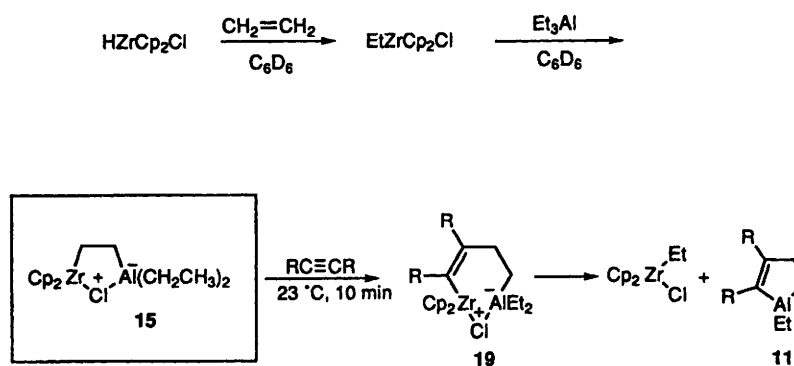


Scheme 22

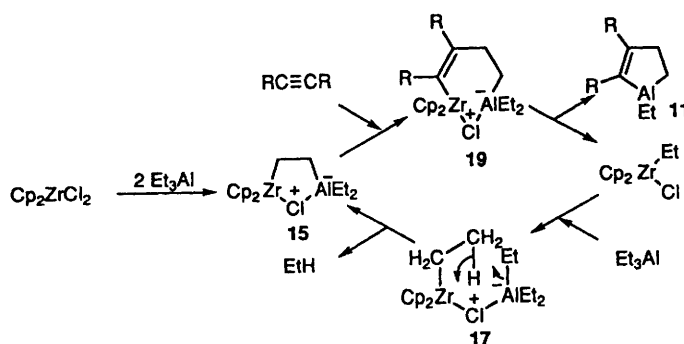
may possibly undergo a more or less thermoneutral double transmetallation to give **11** and  $\text{Et}_2\text{ZrCp}_2$  (Scheme 20). However, we became doubtful about this mechanism, when we failed to detect even a trace of  $\text{Et}_2\text{ZrCp}_2$ . Our doubt became a reality, when addition of **13** (20 mol%) to a 1:3 mixture of dec-5-yne and  $\text{Et}_3\text{Al}$  failed to induce the expected catalytic and cyclic carbometallation reaction. In fact, no reaction was observed. Consequently, the intermediacy of **13** and hence the entire mechanism shown in Scheme 20 must be ruled out.

For clarification of the mechanism of this reaction, a series of detailed earlier studies of the reaction of  $\text{Et}_3\text{Al}$  with  $\text{Cp}_2\text{ZrCl}_2$  by Sinn<sup>36,37</sup> and Kaminsky<sup>37</sup> in the 1960s and 1970s involving NMR and X-ray analyses proved to be very informative. These workers have found that the reaction of  $\text{Cp}_2\text{ZrCl}_2$  with  $\text{Et}_3\text{Al}$  in a 1:1 ratio in  $\text{C}_6\text{D}_6$  rapidly produces a mixture of **14a** and **14b**, which is relatively stable in the absence of an excess of  $\text{Et}_3\text{Al}$ . With an excess of  $\text{Et}_3\text{Al}$ , however, a C–H activation process takes place to give **15** which is subsequently converted to a more stable product **16** via another C–H activation process. The X-ray structure of **16** has also been obtained. We propose that **15** and **16** are formed via **17** and **18**, respectively, by a novel bimetallic  $\beta$  C–H activation followed by ring expansion, as shown in Scheme 21. With these Zr–Al bimetallic species in mind, we carried out the reaction of dec-5-yne with  $\text{Et}_3\text{Al}$  and  $\text{Cp}_2\text{ZrCl}_2$  in benzene under three different sets of conditions as indicated in Scheme 22 and obtained the mono-, di-, and tri-deuterio derivatives of (Z)-5-ethyl-dec-5-ene. Both reaction conditions and the formation of the deuterated product **7** clearly indicate that the reaction of **15** with alkynes is the one which is rel-

evant to the catalytic process. To further probe the course of this reaction, **15** was prepared cleanly in 83% yield by the treatment of  $\text{EtZrCp}_2\text{Cl}$ , preformed by hydrosilylation of ethylene with  $\text{HZrCp}_2\text{Cl}$ , with 1 equiv. of  $\text{Et}_3\text{Al}$ . Since there is no  $\text{Et}_3\text{AlCl}$  in this case, which must interfere with the reaction of  $\text{EtZrCp}_2\text{Cl}$  with  $\text{Et}_3\text{Al}$ , it is considerably faster and cleaner than the reaction of  $\text{Cp}_2\text{ZrCl}_2$  with an excess of  $\text{Et}_3\text{Al}$ . The reaction of **15** prepared from  $\text{EtZrCp}_2\text{Cl}$  and  $\text{Et}_3\text{Al}$ , with dec-5-yne was, as expected, very fast and complete in 10 min at 23 °C to regenerate  $\text{EtZrCp}_2\text{Cl}$  and the expected alane product **11** (Scheme 23). Interestingly, little or no interaction between the two compounds was detectable by NMR



Scheme 23



Scheme 24

spectroscopy. Assuming that the initial carbometallation product of the reaction of dec-5-yne with **15** is **19** (or its regioisomer), a catalytic cycle shown in Scheme 24 may be proposed for the Zr-catalysed reaction of dec-5-yne with  $\text{Et}_3\text{Al}$ . It consists of (i) carbometallation of dec-5-yne with **15** to give **19** or its regioisomer, (ii) Et–alkenyl exchange between Zr and Al species and dissociation to give **11** and  $\text{EtZrCp}_2\text{Cl}$ , (iii) complexation of the latter with  $\text{Et}_3\text{Al}$  to form **17** detectable by NMR spectroscopy, and (iv) its bimetallic C–H activation reaction to regenerate **15**. It is worth mentioning here that carbozirconation of alkenes with Cl-bridged Zr–Al cyclic bimetallic reagents has been recently reported.<sup>38</sup>

A novel and critically significant notion reflected in the catalytic cycle shown in Scheme 24 is a bimetallic  $\beta$  C–H activation process of **17** and **18**, requiring (i)  $\beta$  C–H containing alkylzirconocene moiety, (ii) one Cl atom for tying Zr and Al through a Cl bridge, and (iii) a trialkylalane, e.g.  $\text{Et}_3\text{Al}$ , rather than a di- or mono-alkylalane. The first requirement needs no further comment. The requirement of one Cl atom was originally indicated by the failure to use **13** as a catalyst. To further substantiate this conclusion, 1 equiv of  $\text{Et}_3\text{AlCl}$  was added to **13**. As expected, the reaction produced  $\text{EtZrCp}_2\text{Cl}$  and **11**, and this mixture indeed catalysed the cyclic carboalumination of dec-5-yne with  $\text{Et}_3\text{Al}$ . In this reaction,  $\text{Et}_3\text{AlCl}$  serves as a source of Cl. Evidently, one Cl atom per one Zr atom is needed for the Zr compound to act as a catalyst. Any excess beyond this ratio would become inhibitory. Presumably,  $\text{Et}_2\text{AlCl}$  or  $\text{EtAlCl}_2$  compete for Zr with  $\text{Et}_3\text{Al}$  and produces stable double Cl-bridged bimetallic species, such as **14**, which probably have to be converted to **17** for the formation of **15**. This provides a plausible explanation for the third requirement indicated above.

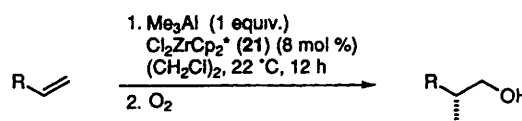
## 7 Zirconium-catalysed Enantioselective Carboalumination of Alkenes

### 7.1 Enantioselective Methylalumination

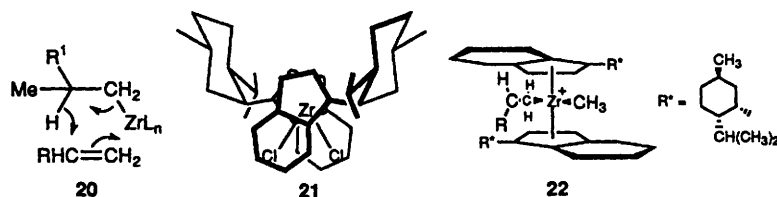
Catalytic enantioselective carbon–carbon bond formation involving simple alkenes without heteroatom functional groups represents a highly desirable but formidable synthetic challenge. One of the ultimate goals in our study in this area has been to achieve enantiose-

lective carbometallation of alkenes under the influence of chiral zirconocene or titanocene derivatives, but our earlier attempts were all unsuccessful. As mentioned in Section 5, the reaction of alkenes with  $\text{Me}_3\text{Al}–\text{Cp}_2\text{ZrCl}_2$  failed to provide the methylalumination products (Scheme 12) due to competitive hydroalumination (Scheme 10). For successful observation of Zr-catalysed methylalumination, all but the initial methylmetallation in Scheme 12 must be effectively blocked. This requires a carbometallation process which is faster than competing hydrometallation and carbometallation processes. Although this appeared to us to be very wishful, we were encouraged by the known asymmetric, if non-enantioselective, Kaminsky-type alkene polymerization reaction,<sup>39</sup> which must proceed *via* a series of carbometallation processes favoured over potentially competitive hydrometallation processes. Provided that such a favourable carbometallation process could be devised, the next key question was if it could be highly enantioselective. We reasoned that such a process for at least methylmetallation would have to involve either four-centred direct carbozirconation similar to that shown in Scheme 6 or six-centred processes similar to those represented by **5** and **6**, preferably the former, for effective alkene face selection.

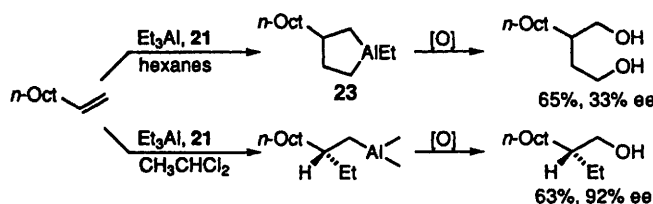
Ironically, all these structural and mechanistic apprehensions were swept away by the surprisingly favourable observation of conversion of oct-1-ene into an 88% yield of (2*R*)-2-methyl-octan-1-ol in 72% ee by the reaction shown in Scheme 25.<sup>23</sup> How does this reaction avoid chiral product-depleting hydrometallation? One possible explanation is that the hydrometallation process may be associative as indicated by **20**, which would be increasingly hindered as the steric requirements of the ligands increase. This point is currently under investigation. Although not certain, the relatively high



Scheme 25



Scheme 26



Scheme 27

% ee figure appears to be consistent with either a four-centred direct carbозirconation process similar to Scheme 6 or a six-centred process similar to that represented by 5. Judging from the observed absolute stereochemistry of the product, Erker's chiral zirconium complex containing 1-neomenthylindene (**21**)<sup>40</sup> must select the *re* face of monosubstituted alkene, provided that the carbometallation step involves a *syn* addition, as indicated in **22** for the four-centred version.

The Zr-catalysed enantioselective methylalumination reaction of monosubstituted alkenes appears to be reasonably general with respect to the carbon groups in alkenes. Both chemical and optical yields are in reasonable ranges, although further improvements are clearly desirable. The reaction also appears to be compatible with certain heteroatom functional groups, such as alcohols and amines. The experimental results obtained with **21** are summarized in Table 1.

## 7.2 Enantioselective Alkylalumination

Having developed the Zr-catalysed enantioselective methylalumination of alkenes, we turned our attention to the development of similar alkylalumination reactions. However, the initial outlook was rather bleak. Our attempts to develop an enantioselective procedure based on Dzhemilev's ethylmagnesium<sup>24</sup> were very disappointing leading only to very low % ee figures. In this connection, however, it is noteworthy that favourable results have been obtained by Hoveyda<sup>41</sup> through the use of special classes of alkenes, *i.e.* cyclic allyl ethers. Dzhemilev<sup>35a,c</sup> also reported recently the Zr-catalysed reaction of monosubstituted alkenes with Et<sub>3</sub>Al producing aluminacyclopentanes (**23**). Unfortunately, however, the reaction of dec-1-ene in the presence of **21** led only to the product of 33% ee (Scheme 27). In an attempt to observe an acyclic alkylalumination process, Et<sub>2</sub>AlCl in conjunction with **21** was used, but the results were very disappointing. Recalling significant solvent effects observed in the carbocationic reaction of alkynes (Section 6), the reaction of dec-1-ene with Et<sub>3</sub>Al (1 equiv.) and a catalytic amount of Cp<sub>2</sub>ZrCl<sub>2</sub> was carried out in (CH<sub>2</sub>Cl)<sub>2</sub>. After deuteration, 3-(deuteriomethyl) undecane was obtained in 37% yield along with a *ca.* 20% yield each of 2-ethyl-dec-1-ene and 1-deuteriododecane. The reaction must have undergone acyclic ethylalumination to the extent of 57%, but a competing hydroalumination reaction must have depleted the ethylalumination product to the extent of 20%. Encouraged by these results, we then ran the same reaction in the presence of **21** in place of Cp<sub>2</sub>ZrCl<sub>2</sub> and observed, for the first time, a favourable ethylalumination which appears to proceed *via* non-cyclic carbometallation<sup>42</sup> (Scheme 27). The use of CH<sub>2</sub>Cl<sub>2</sub> or CH<sub>3</sub>CHCl<sub>2</sub> at 0 °C or, preferably –25 °C, was optimal. As summarized in Table 2, a variety of monosubstituted alkenes have been converted to ethyl- and higher alkyl-aluminated prod-

**Table 1** Zirconium-catalysed methylalumination of monosubstituted alkenes<sup>a</sup>

Substrate	t/h	Product	Yield, <sup>b</sup> %	ee, %
	12		88	72
	12		92	74
	12		80	65
	24		77	70
	528		30	85
	12		81	74
	12 <sup>c</sup>		79	75
	96 <sup>d</sup>		68	71

<sup>a</sup> The reactions were run using 8 mol% of **21**, 1 equiv. of Me<sub>3</sub>Al in 1,2-dichloroethane at 22 °C. <sup>b</sup> Isolated yields. <sup>c</sup> Threefold excess of Me<sub>3</sub>Al was used. <sup>d</sup> Twofold excess of Me<sub>3</sub>Al was used.

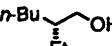
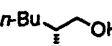
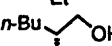
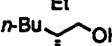
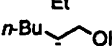
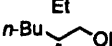
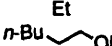
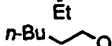
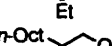
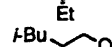
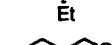

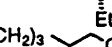
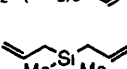
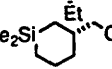
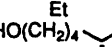
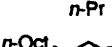
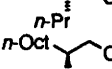
ucts. The observed chemical yields are lower than those of methylalumination by 10–15% presumably due to competitive hydro-metallation, but the % ee figures observed under the optimized conditions were mostly in the 90–95% range. Here again, uniform and predictable *re* face selection has been observed.

## 8 Epilogue

Our odyssey in the area of carbometallation promoted or catalysed by early transition metals started about 20 years ago with very simple and perhaps naive notions, such as those shown in Schemes



**Table 2** Zirconium-catalysed alkylaluminumation of monosubstituted alkenes<sup>a</sup>

Substrate	R of R <sub>3</sub> Al	Solvent	Temp /°C	Time /h	Quenching agent	Product	Yield <sup>b</sup> %	%ee
<i>n</i> -Bu	Et	(CH <sub>2</sub> Cl) <sub>2</sub>	25	4	O <sub>2</sub>		65	68
<i>n</i> -Bu	Et	Cl-C <sub>6</sub> H <sub>5</sub>	25	4	O <sub>2</sub>		70	68
<i>n</i> -Bu	Et	1,2-Cl <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	25	4	O <sub>2</sub>		72	67
<i>n</i> -Bu	Et	CH <sub>2</sub> Cl <sub>2</sub>	25	6	O <sub>2</sub>		57	81
<i>n</i> -Bu	Et	CH <sub>2</sub> Cl <sub>2</sub>	0	6	O <sub>2</sub>		63	92
<i>n</i> -Bu	Et	CH <sub>2</sub> Cl <sub>2</sub>	-25	6	O <sub>2</sub>		60	94
<i>n</i> -Bu	Et	CH <sub>3</sub> CHCl <sub>2</sub>	25	6	O <sub>2</sub>		70	86
<i>n</i> -Bu	Et	CH <sub>3</sub> CHCl <sub>2</sub>	0	24	O <sub>2</sub>		74	93
<i>n</i> -Oct	Et	CH <sub>3</sub> CHCl <sub>2</sub>	0	12	O <sub>2</sub>		64	92
<i>i</i> -Bu	Et	CH <sub>3</sub> CHCl <sub>2</sub>	0	24	O <sub>2</sub>		77	90
Ph	Et	CH <sub>3</sub> CHCl <sub>2</sub>	0	24	O <sub>2</sub>		69	93
HO(CH <sub>2</sub> ) <sub>4</sub>	Et <sup>c</sup>	CH <sub>3</sub> CHCl <sub>2</sub>	10	24	HCl		88	90
Et <sub>2</sub> N(CH <sub>2</sub> ) <sub>3</sub>	Et <sup>d</sup>	CH <sub>3</sub> CHCl <sub>2</sub>	25	72	O <sub>2</sub>		56	95
	Et	CH <sub>3</sub> CHCl <sub>2</sub>	0	24	O <sub>2</sub>		66	96
HO(CH <sub>2</sub> ) <sub>4</sub>	Pr <sup>c</sup>	CH <sub>3</sub> CHCl <sub>2</sub>	10	24	HCl		90	91
<i>n</i> -Oct	Pr	CH <sub>3</sub> CHCl <sub>2</sub>	0	12	O <sub>2</sub>		62	91
<i>n</i> -Pr	Oct	CH <sub>3</sub> CHCl <sub>2</sub>	0	12	O <sub>2</sub>		59	85

The reactions were run using 8 mol% of **21**, 1 equiv. of R<sub>3</sub>Al, unless otherwise stated. <sup>b</sup> Isolated yields. Threefold excess of R<sub>3</sub>Al was used. <sup>c</sup> Twofold excess of R<sub>3</sub>Al was used.

1 and 2. From the beginning it has encountered a series of unexpected results and puzzles, and the results obtained by us and others have almost always been much more varied and intricate than initially thought. Nonetheless, a number of expected and synthetically useful reactions, such as Zr-catalysed carboalumination of alkynes, Zr-catalysed or -promoted hydrometallation of alkenes and alkynes, a wide variety of 'ZrCp<sub>2</sub>'-promoted and -catalysed reactions, and Zr-catalysed enantioselective carboalumination of alkenes, have been discovered and developed. As sometimes stated, simple, naive and imperfect theories and notions are clearly better than no theories and notions, provided that they are fundamentally sound and employed with discretion. After all, Scheme 1 is essentially the same as the better known Dewar–Chatt–Duncanson model, one of the most fundamental theories in organotransition metal chemistry. The only difference is that a  $\sigma$  bond is used as a HOMO in place of a filled unbinding orbital. The synthetic utility of carbometallation in the synthesis of natural and unnatural complex organic molecules has been well founded over the past few decades and has become undisputable. Many additional applications of the reactions and procedures discussed in this review will be forthcoming. At the same time, it is still highly desirable to promote additional methodological and mechanistic investigations so that both academic and industrial synthetic chemists may take full advantage of the carbometallation-based methodology.

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