Some newer aspects of organozirconium chemistry of relevance to organic synthesis. Zr-Catalyzed enantioselective carbometallation*

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Abstract: The reaction of terminal alkenes with trialkylalanes in the presence of chiral $(NMI)_2ZrCl_2$ has been shown to be 70–75% ee for methylalumination and 90–95% ee for ethyl- and higher alkylalumination. It must involve an acyclic bimetallic process. Its scope, limitations, and applications to some natural products syntheses are discussed.

INTRODUCTION

The presence or ready availability of an empty valence-shell metal orbital is the crucial requirement for concerted *syn*-carbometallation [1]. In reality, however, some other factors for activating the carbon–metal bonds may be additionally required. Thus, for example, the Zr-catalyzed carboalumination of alkynes discovered in 1978 [2] requires both Zr and Al at the crucial stage of the reaction [3], and it is thought to involve an activation of a Lewis acidic center by another via $^{\delta+}M^1–X–^{\delta-}M^2$ interaction [1,4]. In contrast, some other carbometallation reactions [5] have been shown to involve zirconacyclopropanes and zirconacyclopropenes as active carbometallating agents [6,7] and their cyclic carbozirconation, but they appear to be monometallic. Yet other reactions have recently been shown to be both bimetallic and cyclic [8]. Carbometallation of alkenes can be further complicated by competitive hydrometallation by the isoalkylmetals [9] produced by the desired carbometallation, in addition to the well-known oligomerization and polymerization. Successful development of a Zr-catalyzed carbometallation of alkenes must therefore avoid competitive hydrometallation, oligomerization, and polymerization. Various possible paths and mechanisms observable in the reactions of organozirconium reagents with alkenes and alkynes are summarized in Table 1. Over the past several years, some Zr-catalyzed enantioselective ethyl- and higher alkylmetallations have been developed [10–12]. However, high % ee figures, e.g., ≥70% ee, have been reported only with allylically heterosubstituted alkenes.

In this account, the discovery, scope, and synthetic applications of a novel Zr-catalyzed enantioselective carboalumination of 1-alkenes with or without heterofunctional groups [13,14], that is discrete from the other related organozirconium reactions mentioned above [10–12], are described.

RESULTS AND DISCUSSION

Zr-Catalyzed enantioselective carboalumination of 1-alkenes

The reaction of 1-alkenes with Me_3Al in the presence of a catalytic amount of $(NMI)_2ZrCl_2$, where NMI is 3-neomenthyl-1-indenyl, has been shown to proceed in good yields and typically in 70–75% ee [13]. It is thought to proceed via an acyclic and bimetallic process, as shown in Scheme 1. Some representa-


Table 1 Mechanisms of carbometallation and related reactions.

| Mode	Monometallic	Bimetallic
Acyclic	Not known with alkylzirconiums (with possible exceptions, *e.g.*, allylzirconation)	$R^1C\equiv CH \xrightarrow[\text{(Negishi, 1978)}]{R^2AlX_2/Cl_2ZrCp_2}$ (alkene product)
Cyclic	• Dzhemilev ethylmagnesiation (1983) • Mechanism clarified by Negishi-Takahashi (1991) $R\diagup\diagup \xrightarrow[\text{cat. } Cl_2ZrCp_2]{EtMgBr}$ (product with Et, MgBr)	• Negishi Zr-Catalyzed Ethyl- and higher alkylalumination (1978) • Mechanism clarified by Negishi (1996) $RC\equiv CR \xrightarrow[\text{cat. } Cl_2ZrCp_2]{Et_3Al}$ (alkene with R, R, Et, AlX_2)
Competitive Hydrometallation	• Hydroalumination (Negishi, 1980) and Hydrozirconation (Negishi, 1984)	• Catalyzed by a large number of Lewis-acidic metal complexes (Negishi, 1999)

tive results are summarized in Table 2. This reaction represents as yet rare examples of catalytic, enantioselective C–C bond-forming reactions of one-point binding. Neither polymerization nor hydrogentransfer hydroalumination competes to detectable extents. The absence of the latter is attributable to the use of sterically hindered Cp derivatives.
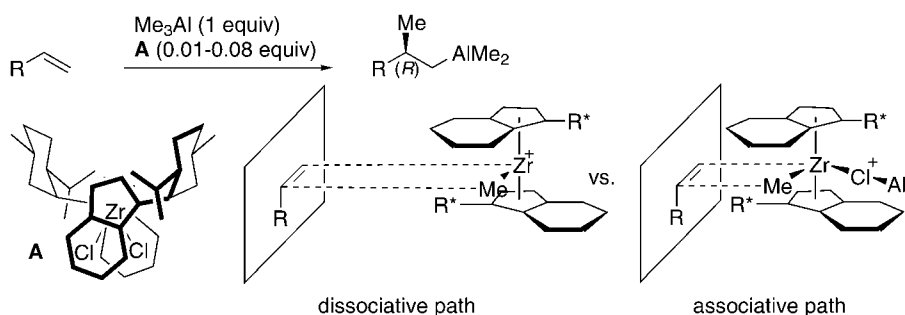
Scheme 1

Table 2 Zirconium-catalyzed enantioselective alkylalumination-oxidation to convert 1-alkenes to 2-alkyl-substituted 1-alkanols with alanes using **A** as a catalyst.

| Substrate	Me₃Al		Et₃Al	
	Yield, %	% ee	Yield, %	% ee
$RCH=CH_2$ ($R = n\text{-}C_4H_9, n\text{-}C_6H_{13}, n\text{-}C_8H_{17}$)	88	72	63–75	90–93
$i\text{-}BuCH=CH_2$	92	74	77	90
$PhCH_2CH=CH_2$	77	70	69	93
$c\text{-}HexCH=CH_2$	80	65		
$HO(CH_2)_4CH=CH_2$	79	75	88	90
$Et_2N(CH_2)_3CH=CH_2$	68	71	56	95

The corresponding reaction with Et₃Al and higher trialkylalanes, which proceeds cleanly and in high yields in nonpolar solvents, produces cyclic alanes, but it is of low enantioselectivity [14]. However, a dramatic mechanistic switch from cyclic to acyclic occurs when chlorinated hydrocarbons, such as CH_2Cl_2, $ClCH_2CH_2Cl$, and somewhat preferably CH_3CHCl_2, are used as solvents, and this reaction can proceed typically in 90–95% ee (Scheme 2). The reaction is accompanied by competitive

hydrometallation to a minor extent, and the yields of the desired carboalumination products are typically 10–15% lower than those of methylalumination. Some representative results are also summarized in Table 2.
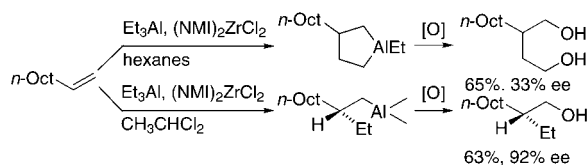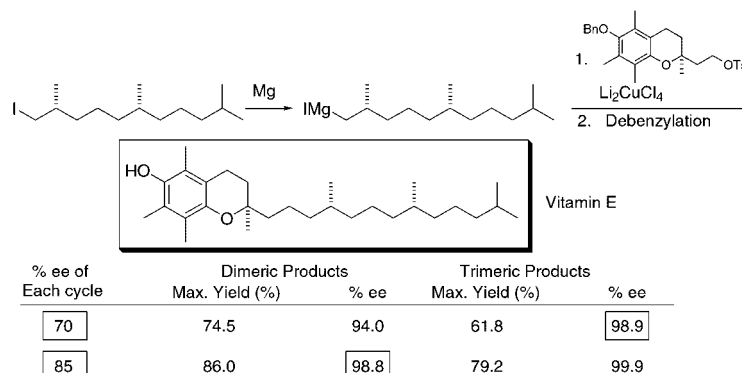

Scheme 2

Several other chiral zirconocene derivatives have also been tested, but none has exhibited higher enantioselectivity. Efforts along this line are ongoing. At the same time, however, applications to the enantioselective synthesis of natural products have also been investigated. As indicated by the synthesis of phytol in five steps from 6-methyl-1-heptene summarized in Scheme 3, highly efficient syntheses of saturated chiral hydrocarbons can be achieved [15]. The two enantioselective steps are 73 and 74% ee. The results indicate that the second enantioselective step is essentially unaffected by the existing asymmetric carbon center, i.e., neither matching nor mismatching. In this connection, it is important to note that enantioselectivity can be significantly enriched by repeating or combining two or more enantioselective processes. For example, production of chiral molecules of 99% ee requires just two steps of 85% ee each or three steps of 70% ee each, and the synthesis of vitamin E in one pot by the known cross-coupling process [16] shown in Scheme 4 [15] cannot only produce vitamin E of >99% ee, but also indicate a ca. 95% ee for the synthesis of phytol.
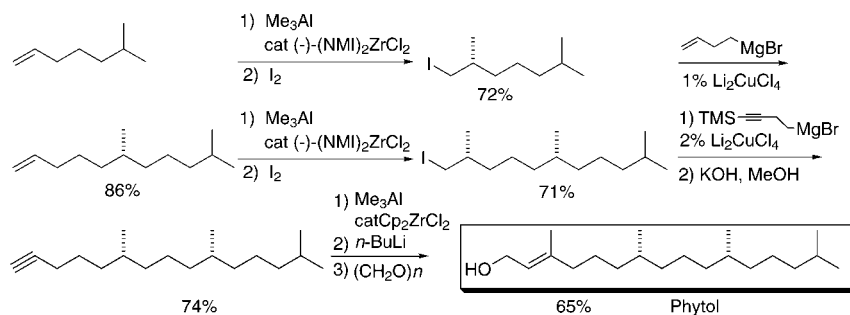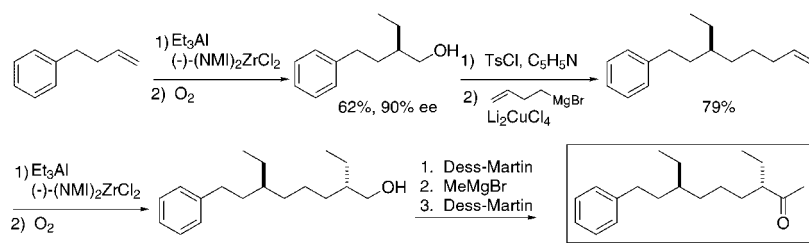

Scheme 3

In an enantioselective synthesis of (3*S*,7*S*)-dianeackerone[17] in seven steps shown in Scheme 5 [15], the enantioselectivity level of ca. 90% each and the 91:9 diasteromeric ratio indicate a ≥99% ee for the product. Efforts are being made to experimentally confirm the ≥99% ee level.

% ee of Each cycle	Dimeric Products		Trimeric Products	
	Max. Yield (%)	% ee	Max. Yield (%)	% ee
70	74.5	94.0	61.8	98.9
85	86.0	98.8	79.2	99.9

Scheme 4

Scheme 5

ACKNOWLEDGMENTS

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