

Zirconium-catalyzed enantioselective carboalumination of “unactivated” alkenes as a new synthetic tool for asymmetric carbon–carbon bond formation*

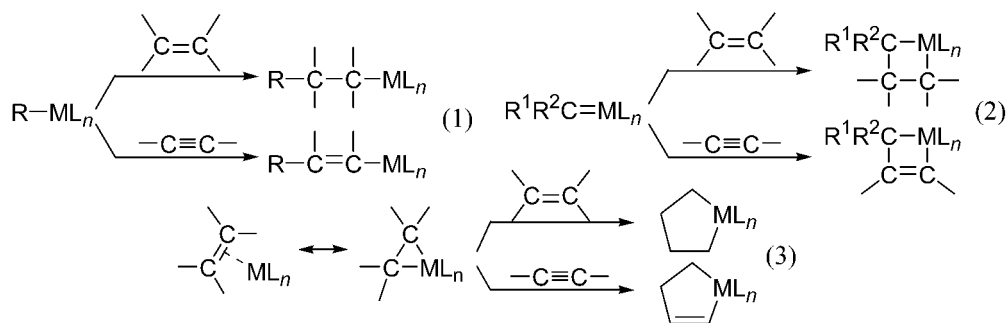
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Abstract: The discovery, methodological developments, including those for separation–purification of chiral flexible primary alcohols, and their applications to the syntheses of some natural products of the titled reaction are discussed.

INTRODUCTION AND BACKGROUND

Carbometallation, a term suggested first in 1978 [1] for a group of insertion reactions involving addition of carbon-metal bonds to alkenes and alkynes, represents one of the several fundamental patterns for C–C bond formation observable with organotransition-metal complexes along with *reductive elimination*, *migratory insertion*, and so on [2,3]. It also embraces alkene and alkyne *metathesis* reactions proceeding via carbometallation of carbon-metal multiple bonds and *cyclometallation* reactions proceeding via carbometallation of metal-alkene and metal-alkyne π -complexes (or metalacyclopropanes and metalacycloprenes) [3] (Scheme 1).



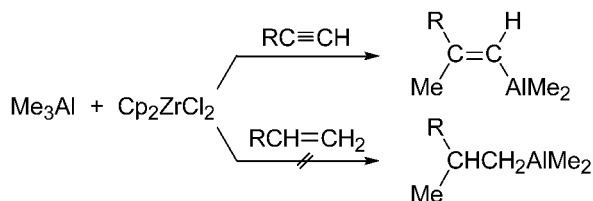
Scheme 1

Earlier examples of carbometallation, such as the Ziegler–Natta polymerization, Reppe synthesis of cyclooctatetraenes from alkynes, and Wilke synthesis of cyclododecatriene from butadiene [3], mostly produced highly symmetric oligomers and polymers. As such, they are of severely limited applicability in the synthesis of natural products and related organic compounds. One of the earliest examples of controlled, single-stage carbometallation is the Normant alkyne carbocupration [2,4]. As useful as it is, difficulties associated with methylcupration have limited its utility in the synthesis of natural products and related organic compounds.

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Over the past couple of decades, the Zr-catalyzed carboalumination of alkynes discovered in 1978 [1] has emerged as a highly selective method for the synthesis of stereodefined alkenes and has been applied to the synthesis of many dozens of complex natural products (Scheme 2). The reaction with Me_3Al and Cp_2ZrCl_2 , where Cp is $\eta^5\text{-C}_5\text{H}_5$, is believed to involve an *acyclic* carbometallation, in which a *bimetallic* $\text{Zr}^{\delta+}\text{-Cl-Al}^{\delta-}$ interaction is important [5]. Disappointingly, early attempts to observe the corresponding reaction of alkenes were unsuccessful.



Scheme 2

In the meantime, however, a seemingly related reaction of ethylmagnesium derivatives with alkenes catalyzed by Cp_2ZrCl_2 was reported by Dzhemilev [6]. Strikingly, this reaction totally failed with methylmagnesium derivatives. Systematic investigations by Negishi and Takahashi [7] of cyclic carbozirconation reactions (eq. 3 in Scheme 1), which appeared totally unrelated to the Dzhemilev reaction [6], have unintentionally clarified the mechanism of the latter, which involves cyclic carbozirconation of $\text{Cp}_2\text{Zr}(\text{CH}_2=\text{CH}_2)$ [7,8].

The currently available data indicate that carbozirconation with alkylzirconocene derivatives may be (i) *acyclic bimetallic* [1,5], (ii) *cyclic monometallic* [7], and even (iii) *cyclic bimetallic* [5,9]. Notably, however, no *acyclic monometallic* carbozirconation with methyl- and other simple alkyl-substituted zirconocene derivatives appears to have been reported. One may tentatively conclude that activation of the C–Zr bond by bimetallic or related polarization of a bond to Zr and/or formation of a strained zirconacycle is necessary for carbozirconation with alkylzirconocene derivatives. Furthermore, the currently available data indicate that those enantioselective carbozirconation reactions which are thought to proceed via cyclic carbozirconation developed since 1993 [10] can lead to high enantioselectivities only when allylically heterosubstituted alkenes, such as allyl alcohols, ethers, and amines, are used. Indeed, simple 1-alkenes, such as 1-octene, have been ethylzirconated in <30–40% ee [11]. Moreover, cyclic carbozirconation requiring a β -H atom would not be applicable to the singularly important case of methylmetallation. Those facts and speculations led us to focus our attention on *acyclic bimetallic* carbometallation for the development of enantioselective alkene carbometallation.

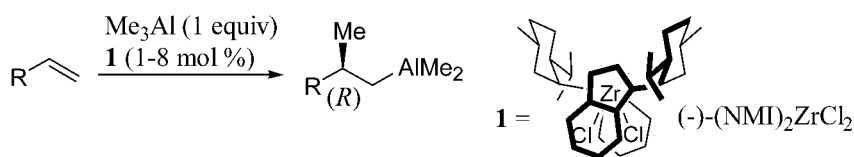
There were at least two additional concerns and barriers to be overcome. One that proved to be a major obstacle was that the desired products of carboalumination of alkenes were isoalkylalanes, which were shown as early as 1980 [12] to be excellent β -H transfer reagents in the presence of Cp_2ZrCl_2 as a catalyst. A more recent investigation [13] has indeed established that this H-transfer hydroalumination is indeed the major side reaction competitively depleting the desired isoalkylalanes. Clearly, this side reaction needs to be substantially suppressed. Another side reaction to be suppressed is the well-known Ziegler–Natta-type alkene polymerization, especially the Kaminsky reaction, which appears to have been reported first in 1976 [14].

RESULTS AND DISCUSSION

Discovery of Zr-catalyzed enantioselective carboalumination of alkenes

Despite all odds that were seemingly against our goal, the desired Zr-catalyzed enantioselective carboalumination of “unactivated” alkenes was finally discovered after repeated and arduous attempts over 17 years. Thus, the reaction of 1-alkenes with Me_3Al in the presence of a catalytic amount of

(NMI)₂ZrCl₂ (**1**) [15], where NMI is 3-neomenthyl-1-indenyl, was shown to proceed in high yields and typically in 70–75% ee [11,16] (Scheme 3). The configuration of the product at the C-2 chiral center is uniformly *R* in cases where **1** is derived from (–)-menthol, and the use of (+)-menthol uniformly led to the *S* isomers. A number of other chiral zirconocene derivatives were also tested, but none was as good and convenient as **1**. Although the precise mechanism of the reaction is not known, the available data are consistent with a mechanism involving an *acyclic bimetallic* process [9,16]. Although further clarification is necessary, the available data indicate that the use of bulky ligands, such as NMI or even indene itself, is primarily responsible for suppressing β-H transfer hydroalumination. Polymerization of alkenes is minimized primarily by the use of just one equivalent or less of an alkene relative to the alkylalane reagent.



Scheme 3

In the ethyl- or higher alkylaluminum, the use of nonpolar solvents, such as hexanes, induced cyclic carboalumination of low ee. However, the use of chlorinated hydrocarbons, such as CH₂Cl₂, ClCH₂CH₂Cl, and CH₃CHCl₂, completely changed the course of reaction from cyclic to acyclic, providing the desired alkylaluminum products in good yields in ≥90% ee [11]. The origin of the significantly higher ee for ethylaluminum (90–95% ee) (Table 1) is not clear. It is, however, possible that Et and higher alkyl groups would exert a secondary chiral induction stemming from α-agostic interaction [17], which is uniquely absent in the case of Me.

Table 1 2-Alkyl-substituted 1-alkanols via Zr-catalyzed alkylaluminum-oxidation.

Substrate	Me ₃ Al		Et ₃ Al	
	Yield, %	% ee	Yield, %	% ee
RCH=CH ₂ (R = <i>n</i> -alkyl)	88	72	63-75	90-93
<i>i</i> -BuCH=CH ₂	92	74	77	90
PhCH ₂ CH=CH ₂	77	70	69	93
<i>c</i> -HexCH=CH ₂	80	65	–	–
HO(CH ₂) ₄ CH=CH ₂	79	75	88 (protonolysis)	90
Et ₂ N(CH ₂) ₃ CH=CH ₂	68	71	56	95

Attempts to optimize the conditions for methylaluminum led to the formation of (*R*)-2-methyl-1-octanol in 82% yield and 81% ee by the reaction of 1-octene with Me₃Al in the presence of **1** in CH₃CHCl₂ [11]. In this connection, a recent report by Wipf [18] describing similar increases by 5–10% ee through rate acceleration by using of H₂O or methylaluminoxane (MAO) is noteworthy. Despite some room for further improvements, an as yet rare catalytic and enantioselective carbon–carbon bond-forming reaction of “unactivated” alkenes (substrates of one-point binding) has become available for use in organic synthesis.

Recent developments

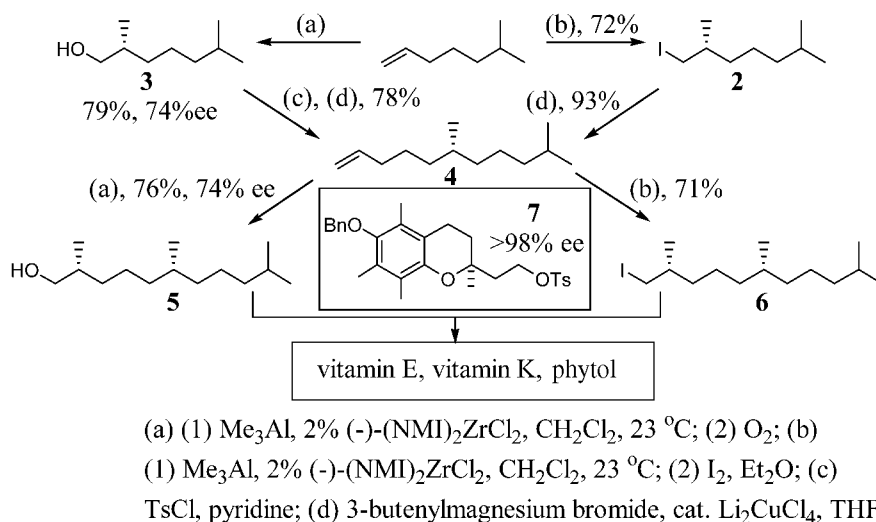
Efficient synthesis of phytol, vitamin E, and vitamin K

Following the discovery discussed above, further developments of the Zr-catalyzed enantioselective carboalumination should preferably entail the following efforts, probably in the indicated order: (1) search for superior chiral zirconocene complexes and optimization of the reaction conditions so as to

attain nearly 100% ee levels, e.g., $\geq 98\%$, and eliminate the need for subsequent stereochemical purification, (2) further exploration of the scope and limitations for various synthetic applications, (3) methodological developments other than the item 1, (4) development of superior methods for diastereomeric separation–purification, and (5) synthetic applications, especially in the area of natural products.

Over the past several years, some serious efforts have been made to find superior chiral zirconocene derivatives, but none has thus far been superior to **1**. In the meantime, simultaneous efforts to explore the other items listed above have been initiated.

To probe the potential synthetic utility of the Zr-catalyzed enantioselective carboalumination, phytol, vitamin E, and vitamin K were chosen as test compounds. The new asymmetric reaction has readily permitted the development of a 3- to 4-step protocol for the synthesis of a C₁₄ chain moiety of the 3 natural products mentioned above from 6-methyl-1-heptene (Scheme 4) [19]. Neither protection–deprotection nor adjustment of the oxidation level was necessary throughout the synthesis. This synthesis should be compared with the current benchmark synthesis of a C₁₅ side chain by Noyori [20], which requires (a) 9–10 steps from myrcene and (b) preparation of isomerically pure (*E*)-trisubstituted alkenes as substrates for asymmetric transformations. These differences are, however, significantly offset by the fact that each of the two asymmetric carbon centers was generated in our synthesis as an 87/13 mixture of the *R* and *S* isomers, corresponding to 74% ee in each step. Although our new synthetic scheme is substantially simpler and more efficient, the ee figures pale in comparison with the $\geq 98\%$ ee's reported by Noyori [20].



Scheme 4

Statistical enantiomeric amplification in skeletal construction

The essentially identical *R/S* ratios of 87/13 attained in the two stereogenic steps in Scheme 4 indicate that the second step is essentially unaffected by the first, and the reaction is therefore subject to a simple statistical treatment, which predicted that the C₁₄ alcohol **5** should be 95.6% ee. Detailed analyses have experimentally established its ee to be 96.7% [19]. Although not experimentally verified, conversion of **5** of 96.7% ee to vitamin E via Cu-catalyzed cross-coupling of the Grignard reagent derived from **5** with **7** ($>98\%$ ee) must have produced vitamin E of $>99.9\%$ ee. These experiments have confirmed a well-established principle of statistical enantiomeric amplification which plays a magic of producing compounds of high ee, in cases where an opportunity exists for repeating two or more stereogenic operations or for meanly combining two or more chiral compounds, even if each operation or

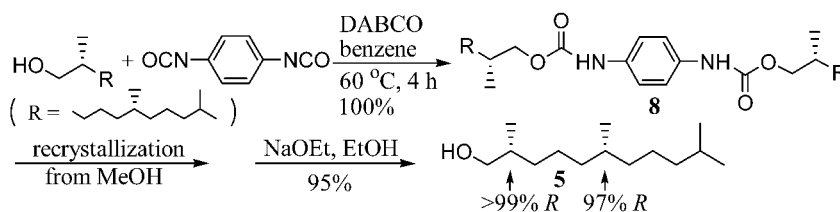
component is $80 \pm 5\%$ ee. There are two practical issues to be resolved, however. One is the separation of the unwanted diastereomers and the enantiomer. The other is a question of how to maintain the yield of the desired product at practically useful levels.

Stereoisomeric separation–purification through statistical amplification

Stereoisomeric purification of flexible primary alcohols having a proximal asymmetric carbon center at the C-2 (rather than C-1) position may have been rarely achieved. In addition to more usual resolution methods, stereoisomeric separation–purification by statistical amplification (the Horeau amplification principle [21]) appeared potentially applicable to the purification of **5**. Survey of the literature indicated that purification of structurally more rigid secondary and tertiary alcohols have been achieved just a few times but that the method has not been applied to the purification of any primary alcohols, let alone highly flexible ones such as **5**.

It was, therefore, gratifying to find that (a) treatment of **5**, in which both asymmetric carbon centers were 87% *R* and 13% *S* (or 74% ee) with a half equiv of *p*-phenylene diisocyanate and DABCO quantitatively yielded a crystalline bisurethane (**8**), (b) it was readily recrystallized from MeOH requiring 0.5–1 h for each cycle, and (c) the material obtained in 33% overall yield after 9 successive recrystallizations followed by basic hydrolysis was >99% *R* at C-2 and 97% *R* at C-6 [19] (Scheme 5). Thus, stereoisomeric purification not only at C-2 but also at C-6 has been achieved.

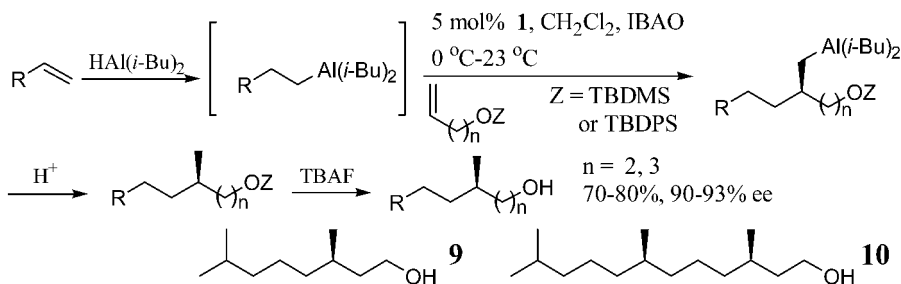
The above results have established the feasibility of purifying delicate mixtures of stereoisomeric primary alcohols containing flexible chains through the formation and recrystallization of bisurethanes derived from an achiral diisocyanate. However, there are still two noticeable shortcomings. One is the need for repeated recrystallization, and the other is the overall recrystallization recovery of 33% or theoretical maximum of 57.3%. All of these shortcomings must primarily stem from the relatively low ee figure of 74% in each stereogenic step.



Scheme 5

New strategy for the synthesis of Me-substituted primary alcohols in high ee

To improve the enantioselectivity in the synthesis of Me-substituted primary alcohols, a new protocol shown in Scheme 6 has just been developed. Its salient features include the following. (1) It takes advantage of the finding that ethyl- and higher alkylaluminumation can proceed in 90–95% ee. (2) The primary alkyl group derived from a monosubstituted alkene by its hydroalumination with DIBAH has a sub-



Scheme 6

stantially higher reactivity than β -branched isobutyl. (3) The aluminomethyl group can be readily hydrolyzed to generate the requisite Me substituent. (4) IBAO (isobutylaluminumoxane) generated *in situ* by treating *i*-Bu₃Al with one molar equivalent of H₂O accelerates the desired carboalumination, while avoiding competitive methylalumination observed with MAO. The desired 3-methyl-1-alkanols have been obtained typically in 70–80% isolated yields and in 90–93% ee [22].

Finally, both **9** and **10** can be readily purified by just a few cycles of recrystallization of the bisurethanes derived from *p*-phenylene diisocyanate to produce **10**, which is $\geq 98\%$ *R* at both C-3 and C-7 centers, in 4 synthetic steps from 4-methyl-1-pentene in 46% overall yield and purified by recrystallization of the bisurethanes derived from **9** and **10**.

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