reaction mixture was concentrated in vacuo. Subsequently, the crude mixture was purified by column chromatography with hexane as eluent to give 1-phenyl-2-propylnaphthalene (**3d**, 106 mg, 0.43 mmol, 62%).

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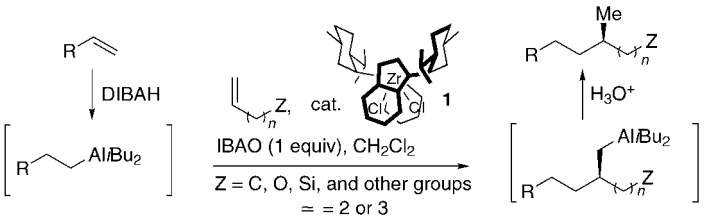
A New Protocol for the Enantioselective Synthesis of Methyl-Substituted Alkanols and Their Derivatives through a Hydroalumination/Zirconium-Catalyzed Alkylalumination Tandem Process**

Shouquan Huo, Ji-cheng Shi, and Ei-ichi Negishi*

We report herein a new protocol for the Zr-catalyzed enantioselective carboalumination of alkenes[1], which consists of a hydroalumination/alkylalumination tandem process (Scheme 1). The most noteworthy significance of the protocol in synthetic applications is that it permits the asymmetric synthesis of methyl-substituted alkanols and other derivatives typically in 90–93% *ee*, which represents an increase in *ee* values by roughly 15% from the previously attainable 70–80%.[1–3]



Scheme 1. Hydroalumination/Zr-catalyzed enantioselective carboalumination/hydrolysis process for the synthesis of methyl-substituted alkanols. IBAO = isobutylaluminoxane.

The development of the protocol has critically depended on the following recent findings. First, the primary alkyl groups of the RCH_2CH_2 type (R = H or alkyl group) derived from $RCH{=}CH_2$ by in situ hydroalumination[4] with iBu$_2$AlH (DIBAH) can participate selectively in the Zr-catalyzed enantioselective carboalumination; these alkyl groups compete directly with two equivalents of the *i*Bu group and the isoalkyl group generated in the desired alkylalumination. As the results summarized in Scheme 2 indicate, the reaction of *n*-decyldiisobutylalane (2 equiv[5]) with $H_2C{=}CH(CH_2)_2OTBDPS$ in the presence of (−)-bis-(neomenthylindenyl)zirconium dichloride[6] (**1**; 5 mol%, purified single isomer) in CH_2Cl_2 followed by protonolysis led to the formation of the desired product **2** in 80–84% yields with 90–91% *ee*.[7] Only traces, if any, of the isobutylaluminated product **3** were formed. Similarly, there was no indication of the formation of dimeric and oligomeric products. The main byproduct was *n*BuOTBDPS, which must have been formed

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by means of H-transfer hydroalumination.[8] On the basis of a reasonable assumption that the *i*Bu group is the major hydride source, *n*Dec is about ten times as reactive as *i*Bu, after statistical correction. Similar results were observed in the reaction of *n*BuAl*i*Bu$_2$ with 1-octene and 1-decene (Scheme 2).[9] In these reactions, however, the hydroalumination products (RCH$_2$CH$_2$Al*i*Bu$_2$), must compete with *n*BuAl*i*Bu$_2$ to give dimeric by-products.[10]

Second, in contrast with the reactions of 1-octene and 1-decene, which were essentially complete within 20 h at 23 °C in the presence of only 2 mol % of **1** without the use of an aluminoxane, the corresponding reactions of 1-alkenes with proximal oxygenated substituents were rather sluggish, presumably as a result of retardation by the oxygenated substituents. The use of methylaluminoxane (MAO)[3] did accelerate these reactions significantly, but methylalumination competed up to 20 %. However, the undesirable methylalumination can be avoided by using isobutylaluminoxane (IBAO),[11] which is generated by treating *i*Bu$_3$Al with H$_2$O (1 equiv). Notably, these aluminoxanes significantly accelerate the Zr-catalyzed carboalumination but they do not significantly affect enantioselectivity under otherwise comparable conditions (Scheme 2). Thus, the improvement in *ee* from 75 ± 5 % to 90 – 93 % is almost entirely a result of the strategic shift from methylalumination to alkylalumination, rather than of the use of aluminoxanes.

Some additional examples of the use of TBS-protected ω-alkenols are shown in Table 1. The results indicate that the TBS-protected 3-butenols and longer ω-alkenols can be alkylaluminated with a variety of alkyldiisobutylalanes to produce, after hydrolysis, the corresponding methyl-substituted alkanols in good yields and 90 – 93 % *ee*. On the other hand, the same reaction of allyl alcohol derivatives ($n = 1$) was unsatisfactory, even when TBDPS-protected allyl alcohol was used as a substrate. Thus, its reaction with *n*-octyldiisobutylalane in the presence of **1** (5 mol %) produced (*R*)-2-methyldecanol only in 30 % yield and with 88 % *ee*. Deprotection of allyl alcohol occurred to a considerable extent. The difficulties and inferior results observed with allyl ethers are in sharp contrast to those observed in the Zr-catalyzed enantioselective ethylmagnesation/β-elimination tandem processes[12] and related reactions[13] of allylic hetero-substituted alkenes. In these reactions, high *ee* values were reported only with allyl ethers, allylamines, and other allylic hetero-substituted alkenes. Clearly the Zr-catalyzed enantioselective carboalumination[1–3] and these carbomagnesation reactions are fundamentally discrete and of almost totally different and complementary synthetic scopes.[14]

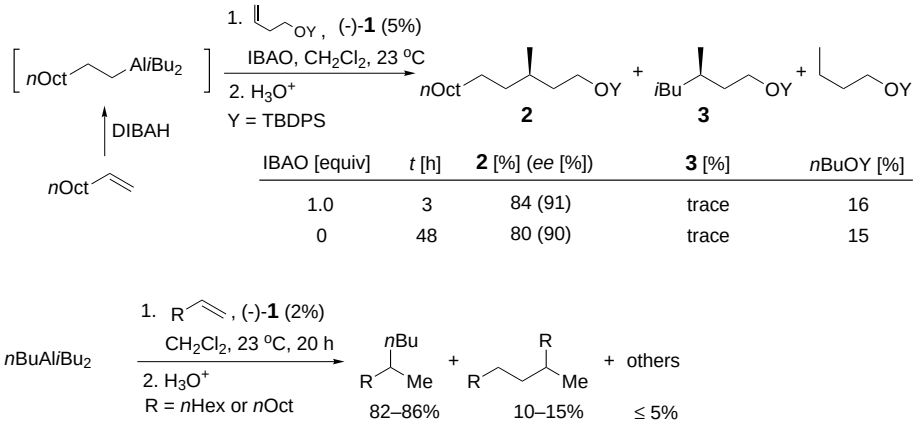
Table 1. Zr-catalyzed enantioselective alkylalumination of ω-alkenyl silyl ethers with alkyldiisobutylalanes.[a]

Entry	R–Al*i*Bu$_2$	$\sim\!\!\sim_n$OTBS	*t* [h]	Yield[b] [%]	*ee*[c] [%]
	R	*n*			
1	*n*-pentyl	2	3	74	92[d]
2	*n*-hexyl	2	3	77	91[d]
3	2-methylpropyl	2	3	82	93[d]
4	4-methylpentyl	2	3	66	91[e]
5	cyclohexyl	2	3	81	91[e]
6	PhMe$_2$SiCH$_2$	2	3	85	90[e]
7	*n*-hexyl	3	6	83	92[f]
8	2-methylpropyl	3	3	78	91[f]
9	*n*-hexyl	4	4	76	90[g]

[a] Unless otherwise stated, the reaction was carried out at 23 °C in CH_2Cl_2 in the presence of **1** (5 mol %) and IBAO (1 equiv). RCH=CH$_2$/DIBAH/H$_2$C=CH(CH$_2$)$_n$OTBS = 1.5:1.5:1. [b] Yield based on the protected enols after protonolysis and deprotection. [c] Determined by HPLC analysis of a derivative of the alcohol (see below) on a CHIRALCEL OD-H or AD (hexane/2-propanol 95:5 or 90:10 v/v). [d] The alcohol was treated successively with $COCl_2$ and (*R*)-1-(1-naphthyl)ethylamine to give the corresponding urethane. [e] The alcohol was oxidized to the corresponding carboxylic acid and then treated with (*R*)-1-(1-naphthyl)ethylamine to give the corresponding amide. [f] As above, except that (*S*)-1-(1-naphthyl)ethylamine was used to produce the amide. [g] This *ee* determination was less accurate than in the other cases (90 ± 2 %). TBS = *tert*-butyldimethyl-

The third critical finding in this investigation is that the enantiomers of methyl-substituted alkanols ($n = 2$, 3) can be detected separately (see Table 1) as well as separated and purified by the recrystallization of their bisurethane derivatives formed in their reaction with *p*-phenylene diisocyanate.[2] Typically, (*R*)-3,7-dimethyl-1-octanol (**4**) of 93 % *ee* (Table 1, entry 3) was treated with *p*-phenylene diisocyanate (0.5 equiv) in benzene at 50 °C for 1 h in the presence of DABCO (1 mol %) to give the corresponding bisurethane (m.p. 118 – 120 °C) in 95 % yield (Scheme 3). After recrystallization from MeOH, it was purified to 96 % *ee* (70 % recovery); m.p. 122.5 – 123.5 °C; $[\alpha]_D^{23} = +3.8°$ ($c = 1.8$, $CHCl_3$).

To demonstrate the synthetic utility of this new protocol, the purified **4** was converted in three steps into **5**,[15] the C_{15} intermediate in the synthesis of vitamin E[16] (Scheme 3). For the synthesis of **4**, a twofold excess of inexpensive 4-methyl-1-pentene relative to H$_2$C=CH(CH$_2$)$_2$OTBS was employed, and the latter was used as the basis to calculate the yield. For the synthesis of **5**, however, (4*R*)-4,8-dimethyl-1-nonene must be used as the limiting reagent. Since a stoichiometric ratio of the two alkene intermediates led only to a 50 % yield of **5**, a 50 % excess of H$_2$C=CH(CH$_2$)$_2$OTBS was employed, which then required the use of *i*Bu$_3$Al



Scheme 2. Selective alkylalumination of 1-alkenes with alkyldiisobutylalanes and rate acceleration effect of IBAO. Y = TBDPS = *tert*-butyldiphenylsilyl.

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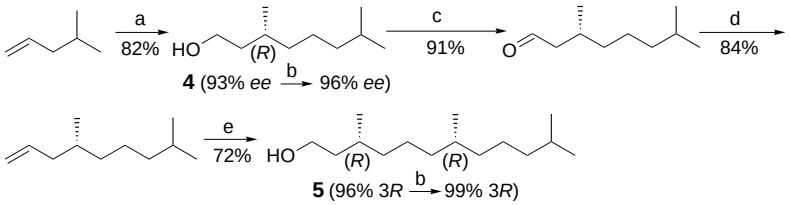

Scheme 3. Synthesis of a C_{15} vitamin E side chain. a) 1. DIBAH, neat, 50 °C, 10 h; 2. $H_2C{=}CH(CH_2)_2OTBS$, **1** (5 mol %), IBAO (1 equiv), 23 °C, 3 h; 3. H_3O^+; 4. TBAF; b) 1. *p*-phenylene diisocyanate (0.5 equiv), DABCO (1 mol %), benzene, 50 °C, 1 h; 2. recrystallization from MeOH; 3. NaOEt/EtOH (2 M); c) DMP, CH_2Cl_2; d) $CH_2{=}PPh_3$, THF; e) 1. DIBAH (1.0 equiv), neat, 60–70 °C, 10 h; 2. $H_2C{=}CH(CH_2)_2OTBS$ (1.5 equiv), **1** (5 mol %), IBAO (1 equiv), *i*Bu_3Al (1.0 equiv), 23 °C, 24 h; 3. H_3O^+; 4. TBAF. TBAF = tetrabutylammonium fluoride, DABCO = 1,4-diazabicyclo[2.2.2]-octane.

(1.0 equiv) as well as IBAO to obtain the indicated yield of 72 %. This four-step synthesis of **5** offers a high efficiency and a respectable combination of overall yield and stereoselectivity that is significantly higher than that reported recently by us.[2]

Although hydroalumination of alkenes with DIBAH is a preferred method for the generation of RCH_2CH_2Al*i*Bu_2, they may also be generated by treating the corresponding alkyllithium compounds with $ClAl$*i*Bu_2 and using them in the Zr-catalyzed carboalumination of alkenes. It should, however, be noted that the LiCl by-product significantly retards the subsequent alkylalumination, thus leading to lower yields of product. It is therefore desirable to remove LiCl by filtration. For example, the reaction of $H_2C{=}CH(CH_2)_2OTBS$ with *n*$HexAl$*i*Bu_2 generated from *n*HexLi and DIBAH under the conditions indicated in Table 1 required 38 h to produce, after hydrolysis, (*R*)-3-methyl-1-nonanol with 89 % *ee* in 76 % yield. When the reaction was run at 0 °C for 96 h, the product was obtained in 59 % yield with 92 % *ee*. On the other hand, filtration of LiCl prior to the reaction led to the formation of the same product in 85 % yield with 89 % *ee* within 20 h. Likewise, the reaction of $H_2C{=}CH(CH_2)_3OTBS$ with *n*Hex-Al*i*Bu_2 produced (*R*)-4-methyl-1-decanol in 74 % yield with 91 % *ee*.

The Zr-catalyzed enantioselective carboalumination of alkenes has now been sufficiently well developed so that a number of its applications to the synthesis of complex natural products and related chiral compounds may be anticipated. Our own efforts along this line are in progress and will be reported in future publications.

Experimental Section

Typical procedure: *n*-Octyldiisobutylalane (prepared in situ by reacting 1-octene (337 mg, 3 mmol) and DIBAH (427 mg, 3 mmol) at 60 °C over 10 h under an argon atmosphere) was added to a solution of dichlorobis(1-neomenthylindenyl)zirconium (**1**; 67 mg, 0.1 mmol) in CH_2Cl_2 (6 mL). The mixture was stirred at 23 °C for 5 min and IBAO (1.0 M in CH_2Cl_2, 2 mL, 2 mmol; prepared by treating triisobutylalane with H_2O (1 equiv) in CH_2Cl_2 at −40 °C for 15 min and then at room temperature for 2 h) was added. After stirring at 23 °C for 5 min, the reaction mixture was cooled to 0 °C with an ice bath, and $H_2C{=}CH(CH_2)_2OTBS$ (370 mg, 2 mmol) was added dropwise to the resultant orange solution with subsequent stirring at 0 °C for 1 h and then at 23 °C for 3 h. The mixture was then treated with HCl (3 N), extracted with diethyl ether (3 × 15 mL), washed with $NaHCO_3$, water, and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was dissolved in THF (4 mL) and treated with TBAF (1.0 M in THF, 3 mL, 3 mmol) at 23 °C for 3 h. After removal of the solvent, the residue was dissolved in a minimum amount of CH_2Cl_2 and subjected to column chromatography (silica gel, hexanes/ethyl acetate 8:1). Evaporation provided (3*R*)-3-methylundecan-1-ol[17] as colorless oil (0.48 g, 78 %). $[\alpha]_D^{23} = +3.1°$ ($c = 2.1$, $CHCl_3$) [Lit. [17] $[\alpha]_D^{25} = +2.98°$ ($c = 3.23$, $CHCl_3$)]; determination of *ee*: (3*R*)-3-methylundecan-1-ol was treated successively with $COCl_2$ and (*R*)-1-(1-naphthyl)ethylamine to produce the corresponding urethane; HPLC analysis of this urethane (Chiralcel OD-H, 4.6 mm × 250 mm, hexane/2-propanol 95:5, 1 mL min^{-1}) showed two peaks ($t_R = 17.1$ and 19.4 min, 95.4:4.6), which were assigned to the *R*,*R* and *R*,*S* diastereomers, respectively (91 % *ee*).

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