Zirconium-Catalyzed Enantioselective Alkylalumination of Monosubstituted Alkenes Proceeding via Noncyclic Mechanism

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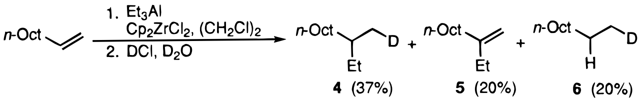
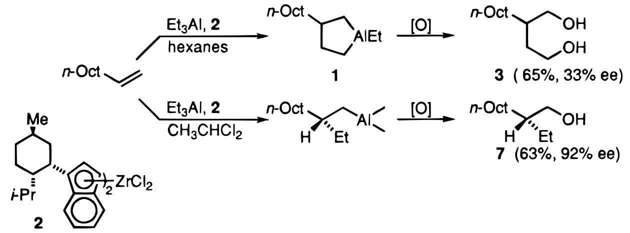
We recently reported a Zr-catalyzed enantioselective methylalumination of monosubstituted alkenes.[1] In contrast, the initial outlook for achieving a similar Zr-catalyzed enantioselective alkylmetalation with ethyl-, propyl-, and higher alkylmetals was not promising. The reaction of monosubstituted alkenes with EtMgX, where X = Cl or Br, in the presence of a catalytic amount of Cp_2ZrCl_2 was known to give (2-ethylalkyl)magnesium halides.[2] The reaction was later shown to proceed via a cyclic mechanism,[3,4] and its successful application to the development of a cyclic enantioselective carbometalation−elimination tandem reaction involving cyclic, allylic ethers and amines has been recently reported.[5] However, attempts to develop Zr-catalyzed enantioselective conversion of monosubstituted alkenes into (2-ethylalkyl)magnesium halides have led only to very disappointing results. Also known was the reaction of monosubstituted alkenes with Et_3Al, catalyzed by Cp_2ZrCl_2, producing aluminacyclopentanes, *e.g.*, **1**,[6] but the reaction of 1-decene with 1 equiv of Et_3Al in the presence of 8 mol % of dichlorobis(neomenthylindenyl)zirconium (**2**)[7] in hexanes produced, after oxidation, a 65% yield of 2-(*n*-octyl)-1,4-butanediol (**3**) in only 33% ee (Scheme 1).

Interestingly, the reaction of 1-decene with 1 equiv of Et_3Al in the presence of 8 mol % of Cp_2ZrCl_2 in $(CH_2Cl)_2$ in place of hexanes produced, after deuterolysis, a 37% yield of 3-(deuteriomethyl)undecane (**4**), which contained D in the C-1 position only to the extent of 9%. The extent of D incorporation in the deuteriomethyl group was >90%. 2-Ethyl-1-decene (**5**) and 1-deuteriodecane (**6**) were also obtained in 20% yield each[8] (eq 1). Although synthetically unattractive, these results clearly indicated that, *in polar solvents, e.g., $(CH_2Cl)_2$, noncyclic ethylalumination similar to methylalumination,[1] partially accompanied by competitive hydroalumination involving a (2-ethyldecyl)alane, can take place in preference to the previously reported cyclic carbometalation processes.*[2−6] Following this intriguing lead, we treated 1-decene with Et_3Al in $(CH_2Cl)_2$ at 25 °C using 8 mol % of **2** as a catalyst and obtained, after oxidation with O_2, a 65% yield of (*R*)-2-ethyl-1-decanol (**7**) in 68% ee. In view of the dramatic solvent effects discussed above, various halogenated solvents were screened, and it was found that the use of CH_3CHCl_2 or CH_2Cl_2 in place of $(CH_2Cl)_2$ boosted the % ee figures to the 80s, and they were further increased to the 90−95% range for various monosubstituted alkenes by merely lowering the reaction temperature to 0 °C. Some representative results are summarized in Table 1. The % ee figures were determined from the ^1H NMR spectra of the (+)- and (−)-MTPA esters. In most cases, the CH_2 group directly bonded to OH showed distinct signals for the two diastereomers. In the cases of (*R*)-2-ethyl-1-hexanol and (*R*)-2-ethyl-1-decanol, the CH_3 signals for the ethyl substituent were used for this purpose. As in the methylalumination with Me_3Al and **2**, alkylmetalation takes place selectively and uniformly on the re face of alkenes.[9] The optimized % ee figures range from 90 to 96% except for one case involving $(n\text{-Oct})_3Al$, where the product was 85% ee. Here again, the presence of remote hydroxy and amino groups may not significantly affect the course of reaction, and diallyldimethylsilane underwent an inter−intra tandem carbometalation exhibiting >92% de and 96% ee stereoselectivity figures. On the other hand, ethylalumination of styrene gave an intractable product, and that of cyclohexylethene did not proceed over 12 h at 25 °C.



(1)

Scheme 1



The highly favorable results observed in ethylalumination in CH_3CHCl_2 prompted us to reexamine the previously reported methylalumination[1] in this solvent. Under otherwise the same conditions, the reaction of 1-octene with Me_3Al in the presence of 8 mol % of **2** at 25 °C in CH_3CHCl_2 gave, after oxidation, an 83% yield of (*R*)-2-methyl-1-octanol in 81% ee, corresponding to an increase by roughly 10% in % ee.[1] Evidently, % ee figures for ethylalumination are 10−15% higher than the corresponding figures for methylalumination under comparable conditions. On the other hand, the yields of ethylalumination are slightly but unmistakably lower than those of methylalumination. A detailed analysis of the products of the above reaction indicated the presence of 3-methylundecane (17%), decane (2%), and the unreacted 1-decene (2%). No more than traces, if any, of 2-ethyl-1-decene and dimeric products were present. Clearly, the lower yield is not due to competitive hydrometalation. Since the results of deuterolysis with $DCl-D_2O$ closely parallel those of oxidation, the origin of 3-methylundecane does not appear to be due to incomplete oxidation. It must have been formed during the carboalumination itself. The use of $(CH_2Cl)_2$ and CH_2Cl_2 led to its formation in 12 and 11%, respectively. The fact that the reaction run in CD_2Cl_2 followed by protonolysis with 3 N HCl does not incorporate D suggests that the solvents

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

[2] Dzhemilev, V. M.; Vostrikova, O. S.; Sultanov, R. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1983**, 219.

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

[4] For related suggestions and studies, see: (a) Hoveyda, A. H.; Xu, Z. *J. Am. Chem. Soc.* **1991**, *113*, 5079. (b) Knight, K. S.; Waymouth, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 6268. (c) Lewis, D. P.; Muller, D. M.; Whitby, R. J.; Jones, R. V. H. *Tetrahedron Lett.* **1991**, *33*, 6797.

[5] Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6997.

[6] Dzhemilev, V. M.; Ibragimov, A. G.; Zolotarev, A. P.; Muslukhov, R. R.; Tolstikov, G. A. *Izv. Akad. Nauk SSSR, Ser. Khim. (Engl. Transl.)* **1989**, 194; **1991**, 2570.

[7] Erker, G.; Aulbach, M.; Knickermeier, M.; Wingbermuhle, D.; Krüger, C.; Nolte, M.; Werner, S. *J. Am. Chem. Soc.* **1993**, *115*, 4590.

[8] The amounts of possible dimeric products, such as 2-(*n*-octyl)-dodecane and 2-(*n*-octyl)-1-dodecene, were ≤1−2%, if any.

[9] The absolute configurations of (*R*)-2-ethyl-1-hexanol (Barth, S.; Effenberger, F. *Tetrahedron Asymmetry* **1993**, *4*, 823), (*R*)-5-methyl-1-octanol (Sonnet, P. E.; Gazzillo, J. A.; Dudley, R. L.; Boswell, R. T. *Chem. Phys. Lipids* **1990**, *54*, 205), and (*R*)-5-methyl-1-heptanol (Chattopadhyay, S.; Mamdapur, V. R.; Chadha, M. S. *Synth. Commun.* **1990**, *20*, 825) were assigned by comparing the observed optical rotation signs and magnitudes with those reported in the literature. The other assignments are more tentative and are based, in part, on empirical predictions [(a) Brewster, J. H. *J. Am. Chem. Soc.* **1959**, *81*, 5475. (b) Marker, R. E. *J. Am. Chem. Soc.* **1936**, *58*, 976)] and experimental observation of optical rotation signs and, in part, on an assumption that the uniform sign of the observed optical rotation is an indication that the face selection remains the same for all cases herein reported.

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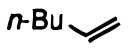
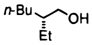
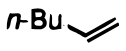
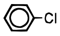
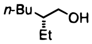
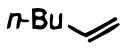
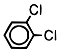
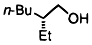
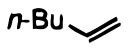
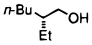
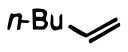
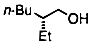
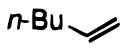
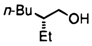
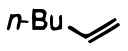
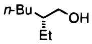
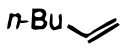
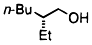
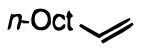
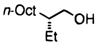
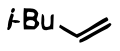
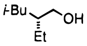
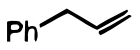
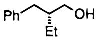
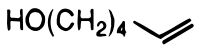
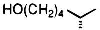
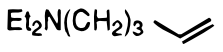
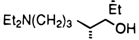
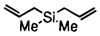
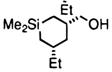
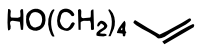
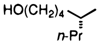
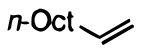
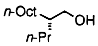
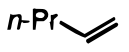
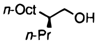
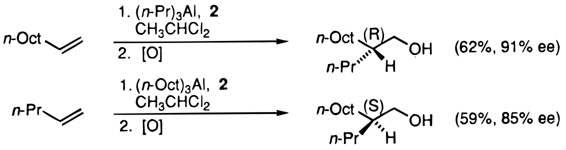
Table 1. Zirconium-Catalyzed Alkylalumination of Monosubstituted Alkenes[a]

substrate	R of R_3Al	solvent	temp °C	time h	quenching agent	product	yield[b] %	%ee
	Et	$(CH_2Cl)_2$	25	4	O_2		65	68
	Et		25	4	O_2		70	68
	Et		25	4	O_2		72	67
	Et	CH_2Cl_2	25	6	O_2		57	81
	Et	CH_2Cl_2	0	6	O_2		63	92
	Et	CH_2Cl_2	-25	6	O_2		60	94
	Et	CH_3CHCl_2	25	6	O_2		70	86
	Et	CH_3CHCl_2	0	24	O_2		74	93
	Et	CH_3CHCl_2	0	12	O_2		64	92
	Et	CH_3CHCl_2	0	24	O_2		77	90
	Et	CH_3CHCl_2	0	24	O_2		69	93
	Et[c]	CH_3CHCl_2	10	24	HCl		88	90
	Et[d]	CH_3CHCl_2	25	72	O_2		56	95
	Et	CH_3CHCl_2	0	24	O_2		66	96
	n-Pr[c]	CH_3CHCl_2	10	24	HCl		90	91
	n-Pr	CH_3CHCl_2	0	12	O_2		62	91
	n-Oct	CH_3CHCl_2	0	12	O_2		59	85

[a] The reactions were run using 8 mol % of **2** and 1 equiv of R_3Al, unless otherwise stated. [b] Isolated yields. [c] Three-fold excess of R_3Al was used. [d] Two-fold excess of R_3Al was used.

are not likely to be the sources of hydrogen. One likely process that might be responsible for the formation of 3-methylundecane is M−H exchange via σ-bond metathesis,[10] although this point needs to be further clarified.

Scheme 2



As expected, the scope of this reaction is not restricted to ethylalumination. Thus, the reaction of 5-hexen-1-ol with 3 equiv of $(n\text{-}Pr)_3Al$ in CH_3CHCl_2 in the presence of 8 mol % of **2** at 10 °C for 24 h provided, after protonolysis, a 90% yield of (*R*)-5-methyl-1-octanol[11] in 91% ee. It is worth noting that the *n*-Pr group of $(n\text{-}Pr)_3Al$ is incorporated as such. Any cyclic processes involving alkene−zirconocene derivatives would incorporate the same group as an *i*-Pr group.[5,12] Both *R* and *S* isomers of 2-(*n*-propyl)-1-decanol can be prepared by *n*-propylalumination of 1-decene and *n*-octylalumination of 1-pentene, respectively, using the same catalyst **2** (Scheme 2).

Acknowledgment. We thank the National Science Foundation (CHE-9402288) for support of this research.

Supporting Information Available: Representative procedure for the synthesis of (*R*)-2-ethyl-1-hexanol; spectral data as well as optical rotation and % ee figures for all isolated products listed in Table 1; and representative ^1H NMR spectra for several compounds (29 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA953655M

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(10) (a) Watson, P. L. *J. Am. Chem. Soc.* **1983**, *105*, 6491. (b) Watson, P. L.; Parshell, G. W. *Acc. Chem. Res.* **1985**, *18*, 51. (c) Fendrich, C. M.; Marks, T. J. *J. Am. Chem. Soc.* **1984**, *106*, 2214. (d) Piers, W. E.; Shapiro, P. J.; Bunel, E. E.; Bercaw, J. E. *Synlett* **1990**, 74 and references therein.

(11) Sonnet, P. E.; Gazzillo, J. A.; Dudley, R. L.; Boswell, R. T. *Chem. Phys. Lipids* **1990**, *54*, 205.

(12) For general discussion of $ZrCp_2$-promoted alkyl−alkene coupling, see: (a) Swanson, D. R.; Rousset, C. J.; Negishi, E.; Takahashi, T.; Seki, T.; Saburi, M.; Uchida, Y. *J. Org. Chem.* **1989**, *54*, 3521. (b) Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124.