A Highly Stereospecific Isomerization of Oxiranes into Allylic Alcohols by Means of Organoaluminum Amides[1]

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Organoaluminum reagents of type $R^1R^2NAlR_2$ allow highly stereospecific oxirane ring opening producing allylic alcohols under mild conditions. *trans*-Epoxycyclododecane is converted to (*E*)-2-cyclododecen-1-ol by reaction with diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP) in quantitative yield, while the *cis*-isomer gives only 8% yield of the same alcohol. Furthermore, this reagent enables us to perform the stereospecific isomerization of trisubstituted oxiranes: *c*-3-butyl-2-methyl-*r*-2-pentyloxirane is transformed into 2-pentyl-1-hepten-3-ol and the diastereomeric oxirane into (*E*)-6-methyl-6-undecen-5-ol, respectively. Such a rigorous stereospecificity is rationalized on the basis of a concerted syn elimination *via* the boat-like six membered ring imtermediary stage, in which the substituents of the oxirane ring should be arranged so as to minimize the severe nonbonded interactions.

A variety of synthetic methods have been developed to bring about the introduction of the allylic alcohol moiety.[2] Among them oxirane-allylic alcohol conversion by means of a strong base offers the advantage of wide spread applicability and experimental simplicity to a unique degree.[3-7] While lithium diethylamide has been widely used for this reaction, the rather vigorous conditions required decrease its practicability.[4-6] A further limitation arises in the reaction with unsymmetrical oxiranes and this reagent is rather nonspecific in the sense that the side chain methyl usually contributes proton to be removed. Accordingly the double bond of the resulting allylic alcohol is located rarely on the main chain. These facts led us to search for a new reagent allowing stereospecific isomerization of oxiranes into allylic alcohols under mild conditions which forms the subject of this paper.

Our attention has been focused on organoaluminum amides, since organoaluminum compounds in general are markedly strong Lewis acids and many of them are known to form stable 1 : 1 complexes with neutral bases such as amines or even ethers. In addition, the aluminum-nitrogen bond is cleaved readily by the attack of proton bearing base such as alcohol to leave aluminum-oxygen bond.[8] It was anticipated that an aluminum amide should be active with respect to both the oxirane ring and the proton to be removed simultaneously.

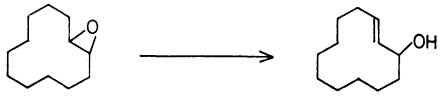
A series of dialkylaluminum *N,N*-dialkylamides were prepared *in situ* from (1) diethylaluminum chloride and lithium amides[9] obtained from secondary amines and butyllithium,[10] or from (2) diisobutylaluminum hydride and amines.[11] Reactions with *trans*-epoxycyclododecane (**1**)[7] under mild conditions (0 °C, 1 h) are summarized in Table 1. Best results were obtained upon the use of four equiv. of diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP) in benzene or hexane.[12] Other aluminum amides also gave (*E*)-2-cyclododecen-1-ol (**2**) as a sole product, however the rates of conversion were lower than that observed with DATMP. Thus the reactivity of alminum amides is apparently dependent on the structure of amine component.[13] Either benzene or hexane proved to be effective, as these do not solvate the aluminum species.[14]

Table 1. Conversion of **1** to **2** by various aluminum amides[a]

Aluminum amide[b]	Solvent	Yield (%)[c]
Et_2Al–TMP[d]	benzene	99
Et_2Al–TMP	hexane	99
Et_2Al–TMP	ether	76
Et_2Al–TMP	tetrahydrofuran	5
Et_2Al–N(*i*-Pr)$_2$[d]	benzene	65
Et_2Al–N(Cy)$_2$[d]	benzene	36
Et_2Al–NEt_2[d]	benzene	5
(*i*-Bu)$_2$Al–NPh_2[e]	benzene	48
(*i*-Bu)$_2$Al–NMePh[e]	benzene	69
(*i*-Bu)$_2$Al–N(*i*-Pr)$_2$[e]	benzene	30

a) For detailed reaction conditions, see Experimental part. b) Abbreviations used here are in accordance with those cited in Ref. 10. c) Yields are based on material isolated by preparative TLC. d) Prepared from diethylaluminum chloride and the corresponding lithium amide at 0 °C for 30 min. e) Prepared from diisobutylaluminum hydride and the corresponding amine.

Remarkably, the *cis* isomer **3** ($n=10$) reacted very reluctantly with DATMP under the same conditions (8 % yield of **2**). In addition, attempts to obtain allylic alcohols from medium ring-attached oxiranes **3** ($n=3$, 4, 5, and 6) were unsuccessful. Most of starting oxiranes were recovered unchanged.



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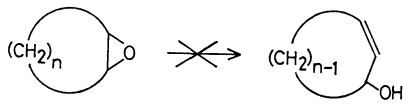

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A few examples illustrate the efficient conversion of oxiranes to allylic alcohols in the presence of DATMP.

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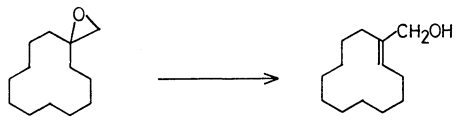
The oxirane **4** was smoothly converted to **5** in 92% yield, while in contrast the reaction with lithium amide yielded less than 5 % of **5**. Oxiranes **6**[7] and **8**[15] gave allylic alcohols **7** and **9** in 98 and 96% yield, respectively. Notably, none of cyclized byproducts was produced in these two cases.



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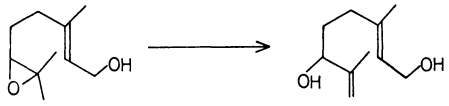

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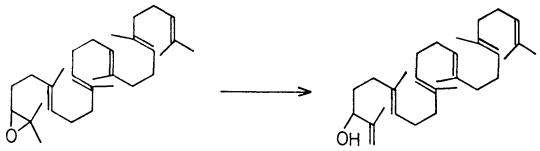

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With the demonstration of the facility and effectiveness of this reagent, attention was directed toward the orientational selectivity in the reaction of unsymmetrical trisubstituted oxiranes. Remarkably, DATMP did react with oxiranes **10** and **12** under sharp discrimination of the configuration of oxiranes. Thus, the reaction of DATMP with oxirane **10** in benzene at 0 °C for 30 min gave the disubstituted allylic alcohol **11** in 96% yield. In marked contrast, the diastereomeric oxirane **12**[16] gave under the same conditions the trisubstituted (*E*)-allylic alcohol **13** predominantly in 83% yield. The structure of the product was unambiguously confirmed by the alternative synthesis of **13** and **14** by means of the β-oxido ylide technique.[17]

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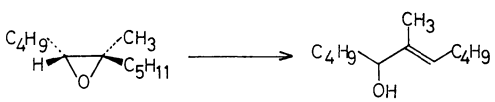

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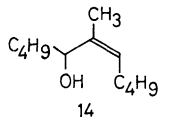

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Aluminum amides preferentially abstract α-proton of the alkyl group located on the same side as hydrogen of oxirane to give the corresponding allylic alcohols (see Fig. 1). This is attributed to the attack of the aluminum reagent from the less hindered side of the oxirane group ("steric approach control"). This is supported by the

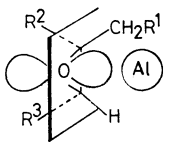
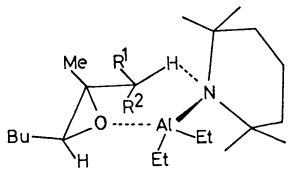


Fig. 1.

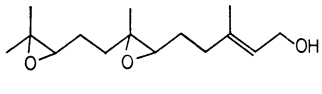


Conformer A (R^1=Bu, R^2=H)
B (R^1=H, R^2=Bu)

Fig. 2.

above finding that only sluggishly *cis*-2,3-disubstituted oxiranes **3** reacted with DATMP. In addition, the resulting allylic double bond prefers the (*E*)-configuration. Such significantly high stereoselectivity observed with DATMP is rationalized by presuming intermediary stage illustrated in Fig. 2 with respect to the reaction of the oxirane **12** with DATMP. Of the possible conformers, the chair ones should suffer from substantial steric interference because of the bulk of the extremely large TMP group. Moreover, of the two boat conformers (A and B), obviously the conformer A has the least steric crowdedness and the subsequent collapse would certainly furnish trisubstituted (*E*)-allylic alcohol **13**. The conformer B has severe crowdedness below the six-membered plane and this explains the minor amount of (*Z*)-allylic alcohol **14**.

Such a remarkable selectivity inherent in DATMP is further demonstrated by the following example. Bisoxirane **15** gives triol **16** upon exposure to lithium diethylamide,[18] while treatment of **15** with DATMP has converted it to the isomeric triol **17**[19,20] in 41% yield.



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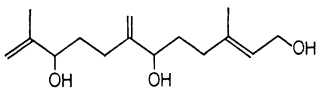

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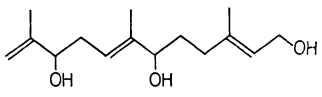

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The selection rules of the DATMP isomerization of oxiranes into allylic alcohols are therefore:

(1) The sole product is a secondary allylic alcohol.

(2) The required proton is supplied by the alkyl group located on the same side as hydrogen of oxirane C(3).

(3) The resulting double bond prefers the (*E*) configuration.

Experimental

The infrared spectra were determined on a Shimadzu IR-27-G spectrometer; the mass spectra on a Hitachi RMU-6L mass machine; the GLPC analyses on a Yanagimoto GCG-550F; and NMR spectra on a JNM-PMX 60 or Varian EM-360 spectrometer. The chemical shifts are given in δ in ppm with TMS as the internal standard. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The microanalyses were carried out by the staffs at the Elemental Analyses Center of Kyoto University. All experiments were carried out under an atmosphere of dry argon. In experiments requiring dry solvents, tetrahydrofuran was distilled from sodium-benzophenone. Ether, benzene, and hexane were dried over sodium metal. During workup, drying of the organic solution was performed over anhydrous sodium sulfate. Thin layer or preparative thick layer plates were made of E. Merck PF-254, and preparative column chromatography on silica gel E. Merck Art. 7734.

Preparation of Dialkylaluminum N,N-*Dialkylamides. From Diethylaluminum Chloride and Lithium Amides*:[9] A benzene solution of diethylaluminum chloride (1 equiv) was added at 0 °C dropwise to a solution of lithium *N,N*-dialkylamide (1 equiv) in benzene. The resulting slurry was stirred at the same temperature for 30 min and used immediately. The following aluminum amides were prepared by this method: diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP); diethylaluminum diisopropylamide; diethylaluminum diethylamide.

From Diisobutylaluminum Hydride and Amines:[11] Diisobutylaluminum hydride (1 equiv) dissolved in benzene was added drop by drop to a solution of amine (1 equiv) in benzene at 0 °C. The resulting solution was gently heated until theoretical volume of hydrogen gas was evolved. The reaction mixture was allowed to cool to 0 °C and then used immediately. The following aluminum amides were prepared by this method: diisobutylaluminum diphenylamide; diisobutylaluminum *N*-methylanilide; diisobutylaluminum diisopropylamide.

*Preparation of Oxiranes. 1-Oxaspiro[2,11]tetradecane (**4**)*: To a mixture of methylenecyclododecane[21] (540 mg, 3.0 mmol) and dichloromethane (15 ml) *m*-chloroperbenzoic acid (712 mg, 3.3 mmol) was added at 0 °C in small portions. The whole mixture was stirred at the same temperature for 1.5 h. After dilution with ether, the mixture was poured into ice-cold saturated sodium sulfite. The separated organic phase was washed with saturated sodium sulfite and saturated sodium bicarbonate, dried, and concentrated *in vacuo*. The residue was submitted to column chromatography using 10: 1 hexane–ether as an eluent to give 534 mg (91% yield) of pure **4** as a clear oil: bp 90 °C (bath temp, 1 Torr); TLC, R_f 0.28 (5: 1 hexane–ether); IR (neat), 2940 (s), 1470 (s), 1445 (m), and 1150 cm^{-1} (w); NMR (CCl_4), 2.39 (2H, s, CH_2–O); MS (*m/e*), 196 (13), 178 (12), 153 (25), 125 (70), and 111 (100).

Found: C, 79.3; H, 12.3%. Calcd for $C_{13}H_{24}O$: C, 79.5; H, 12.3%.

c-*3-Butyl-2-methyl*-r-*2-pentyloxirane (**10**)*. A solution of (*Z*)-6-methyl-5-undecene[16] (250 mg, 1.50 mmol) in dichloromethane (8 ml) was treated with *m*-chloroperbenzoic acid (354 mg, 1.65 mmol) as described above to furnish **10** (250 mg, 90 % yield) as a colorless liquid: bp 64 °C (1 Torr); TLC, R_f 0.65 (1: 1 hexane–ether); IR (neat), 1470 (s), 1370 (s), and 1115 cm^{-1} (m); NMR (CCl_4), 1.19 (3H, s, CH_3–CO), and 2.48 (1H, bt, CH–O); MS (*m/e*), 184 (13), 155 (4), 141 (38), 127 (12), and 71 (100).

Found: C, 78.2; H, 13.4%. Calcd for $C_{12}H_{24}O$: C, 78.2; H, 13.1%.

Reaction of Oxiranes with Aluminum Amides. A General Procedure: To a stirred mixture of aluminum amide (4.0 mmol) and benzene (10 ml) a solution of oxirane (1.0 mmol) in benzene (3 ml) was added at 0 °C drop by drop over a period of 5 min. The whole mixture was stirred at the same temperature until oxirane could not be detected by TLC analysis. The reaction was quenched by the addition of ice-cold 1 M hydrochloric acid and the resulting organic phase was separated. The aqueous layer was extracted with ether. The organic solutions were combined, washed with saturated brine, dried, and concentrated *in vacuo*. The residue was submitted to preparative TLC to give the desired allylic alcohol.

*(E)-2-Cyclododecen-1-ol (**2**)*:[6] TLC, R_f 0.22 (2: 1 hexane–ether); IR (neat), 3330—3370 (s), 1465 (s), 1450 (m), and 970 cm^{-1} (s); NMR (CCl_4), 3.73—4.20 (1H, m, CH–OH), and 4.97—5.82 (2H, m, CH=); MS (*m/e*), 182 (16), 164 (13), 139 (32), 125 (46), and 98 (100).

*1-Cyclododecenylmethanol (**5**)*: This is an (*E,Z*)-mixture, bp 110 °C (bath temp, 1 Torr); TLC, R_f 0.40 (1: 1 hexane–ether); IR (neat), 3300—3360 (s), 1665 (w), 1470 (s), 1000—1010 (s), and 800 cm^{-1} (w); NMR (CCl_4), 3.96 and 4.10 (2H, s, CH_2–O), and 5.15—5.71 (1H, m, CH–); MS (*m/e*), 196 (19), 178 (6), 149 (8), 109 (35), and 83 (100).

Found: C, 79.3; H, 12.5%. Calcd for $C_{13}H_{24}O$: C, 79.5; H, 12.3%.

A small aliquot of **5** was acetylated by stirring with acetic anhydride in pyridine. GLPC analysis (10 % Apiezon, 230 °C, 1.3 kg/cm^2) showed a 69: 31 mixture of (*E*) and (*Z*)-allylic acetates.

*(E)-3,7-Dimethyl-2,7-octadiene-1,6-diol (**7**)*:[22] The title compound was prepared according to the general procedure, except the use of 5 equiv. of DATMP; TLC, R_f 0.28 (ether); IR (neat), 3340—3400 (s), 1650 (m), 1440 (m), 1000 (s), and 890 cm^{-1} (s); NMR ($CDCl_3$), 1.67 (3H, s, CH_4–C= on C-3), 1.73 (3H, s, CH_3–C= on C-7), 3.87—4.23 (3H, d and t, CH–O and CH_2–O), 4.90 (2H, bd, CH_2=), and 5.43 (1H, bt, CH=); MS (*m/e*), 152 (2), 134 (10), 119 (30), 84 (95), and 67 (100).

*(E,E,E,E)-2,6,10,15,19,23-Hexamethyltricosa-1,6,10,14,18,22-hexaen-3-ol (**9**)*: Bp 195 °C (bath temp, 0.5 Torr); TLC, R_f 0.45 (1: 1 hexane–ether); IR (neat), 3400—3480 (m), 1710 (m), 1450 (s), 1380 (s), and 895 cm^{-1} (m); NMR (CCl_4), 3.92 (1H, bt, CH–O), and 4.60—5.33 (7H, m, CH= and CH_2=).

Found: C, 84.6; H, 11.7 %. Calcd for $C_{30}H_{50}O$: C, 84.4; H, 11.8 %.

*2-Pentyl-1-hepten-3-ol (**11**)*: Bp 105 °C (bath temp, 1 Torr); TLC, R_f 0.64 (30: 1 benzene–ethyl acetate, 3 developments); IR (neat), 3310—3400 (s), 1650 (m), 1465 (s), 1015 (s), and 895 cm^{-1} (s); NMR (CCl_4), 3.97 (1H, m, CH–O), 4.80 and 4.96 (2H, s, CH_2=); MS (*m/e*), 184 (2), 155 (3), 127 (15), 113 (25), and 71 (100).

Found: C, 78.1; H, 13.0%. Calcd for $C_{12}H_{24}O$: C, 78.2; H, 13.1%.

*(E)-6-Methyl-6-undecen-5-ol (**13**)*. A sample free from **11** was produced by preparative TLC purification (30: 1 benzene–ethyl acetate, 3 developments): bp 105 °C (bath temp, 1 Torr); TLC, R_f 0.55 (30: 1 benzene–ethyl acetate, 3 develpments); IR (neat), 3310—3400 (s), 1470 (s), 1010 (s), and 850 cm^{-1} (w); NMR (CCl_4), 1.60 (3H, s, CH_3–C=), 3.90 (1H, bt, CH–O), and 5.33 (1H, t, CH=); MS (*m/e*), 184 (4), 155 (8), 127 (66), 109 (30), and 71 (100).

Found: C, 78.0; H, 13.1%. Calcd for $C_{12}H_{24}O$: C, 78.2; H, 13.1%.

A small aliquot was acetylated with Ac_2O–pyridine. GLPC analysis (10% Apiezon, 210 °C, 1.0 kg/cm^2) showed that the product was $>$96 % pure.

Alternative Synthesis of a Mixture of ***13*** *and* ***14***.[17] To a slurry of ethyltriphenylphosphonium bromide (2.32 g, 6.0 mmol) in THF (10 ml) was added dropwise butyllithium (4.6 ml of a 1.3 M hexane solution, 6.0 mmol) at 0 °C. After stirring at 0 °C for 30 min, the resulting red ylide solution was cooled to −78 °C and treated with pentanal (516 mg, 6.0 mmol) dissolved in THF (5 ml). Butyllithium (4.6 ml of a 1.3 M hexane solution, 6.0 mmol) was added dropwise at this temperature to effect immediate red coloring. To this solution was added pentanal (516 mg, 6.0 mmol) dissolved in THF (5 ml), and the solution was brought to room temperature and stirred for 2 h. The reaction mixture was poured into ice-cold water, and the product was extracted with ether. The ethereal solution was dried and freed of the solvent to leave a crude oil, which was purified by preparative TLC (4: 1 hexane–ether) to furnish a mixture of **13** and **14** (820 mg, 74% yield). GLPC analysis as described above showed the ratio of **13**: **14** 84: 16.

*(E,E)-3,7,11-Trimethyldodeca-2,7,11-triene-1,6,10-triol (****17****)*: The title compound was prepared from **15** by the reaction of 10 equiv. of DATMP in benzene at 0 °C for 3 h: TLC, R_f 0.25 (ether); IR (neat), 3260—3400 (s), 1650 (m), 1450 (s), 1000 (s), and 900 cm^{-1} (m); NMR ($CDCl_3$), 1.64—1.80 (9H, bs, CH_3–C=), 3.83—4.69 (4H, m, CH_2–O and CH–O), 4.80—5.12 (2H, d, CH_2=), and 5.20—5.77 (2H, m, CH=).

The microanalysis was performed after trimethylsilylation of both hydroxyl groups.

Found: C, 61.5; H, 10.5%. Calcd for $C_{21}H_{50}O_3Si_3$: C, 61.3; H, 10.6%.

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19) The (*E*) configuration of the central double bond was assumed on the basis of the stereochemical outcomes of other examples, since NMR analysis was not effective enough in this case.

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