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ASYMMETRIC REDUCTION OF ACETOPHENONE WITH CHIRAL REAGENTS FROM LITHIUM TETRAHYDROALUMINATE AND CHIRAL 1,2-DIOL OR DIAMINE AS STUDIED BY ALUMINUM-27 NUCLEAR MAGNETIC RESONANCE

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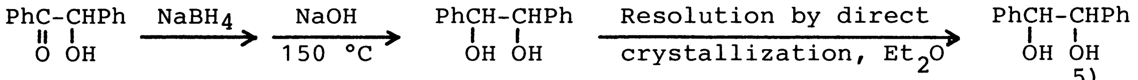
Asymmetric reduction of acetophenone with chiral reagents from lithium tetrahydroaluminate and (1S,2S)-1,2-diphenylethanediol or (1S,2S)-N,N'-diethyl-1,2-diphenylethanediamine in the presence or absence of added ethanol is studied by aluminum-27 NMR spectroscopy.

Asymmetric reductions of prochiral carbonyl compounds with chiral hydride reagents have been extensively studied. Most of the chiral hydride reagents have been obtained by the reaction of lithium tetrahydroaluminate and chiral ligands such as chiral amines, aminoalcohols, or diols etc.1) The dependence of the optical yield of the product alcohol on the structure of ligands and reagents has not clearly explained. In the course of our study about such asymmetric reductions, we observed that the addition of achiral alcohol such as ethanol increased the optical yield of alcohol in case of using a diol or aminoalcohol as a chiral ligand, but not in case of using a diamine.2) In this paper we wish to report the difference between the diamine and diol or aminoalcohol as a ligand for lithium tetrahydroaluminate studied by aluminum-27 nuclear magnetic resonance.

(1S,2S)-1,2-Diphenylethanediol(**1**) and (1S,2S)-N,N'-diethyl-1,2-diphenylethanediamine(**2**) were chosen as chiral ligands, for the molecular configuration are similar each other except the coordinating functional groups: **1** has hydroxy groups while **2** has ethylamino groups. The preparations of **1**2,3) and **2**4) were accomplished according to the known procedure as shown in Scheme 1. Acetophenone was reduced by lithium tetrahydroaluminate, **1** or **2** and/or ethanol in a molar ratio of 4:10:11:(11) according to the reported procedure.2)



$$\underset{\mathrm{O}\quad\mathrm{OH}}{\mathrm{PhC{-}CHPh}} \xrightarrow{\mathrm{NaBH_4}} \xrightarrow[150\ ^\circ\mathrm{C}]{\mathrm{NaOH}} \underset{\mathrm{OH}\ \ \mathrm{OH}}{\mathrm{PhCH{-}CHPh}} \xrightarrow[\text{crystallization, Et}_2\text{O}]{\text{Resolution by direct}} \underset{\mathrm{OH}\ \ \mathrm{OH}}{\mathrm{PhCH{-}CHPh}}$$

15)

Scheme 1.

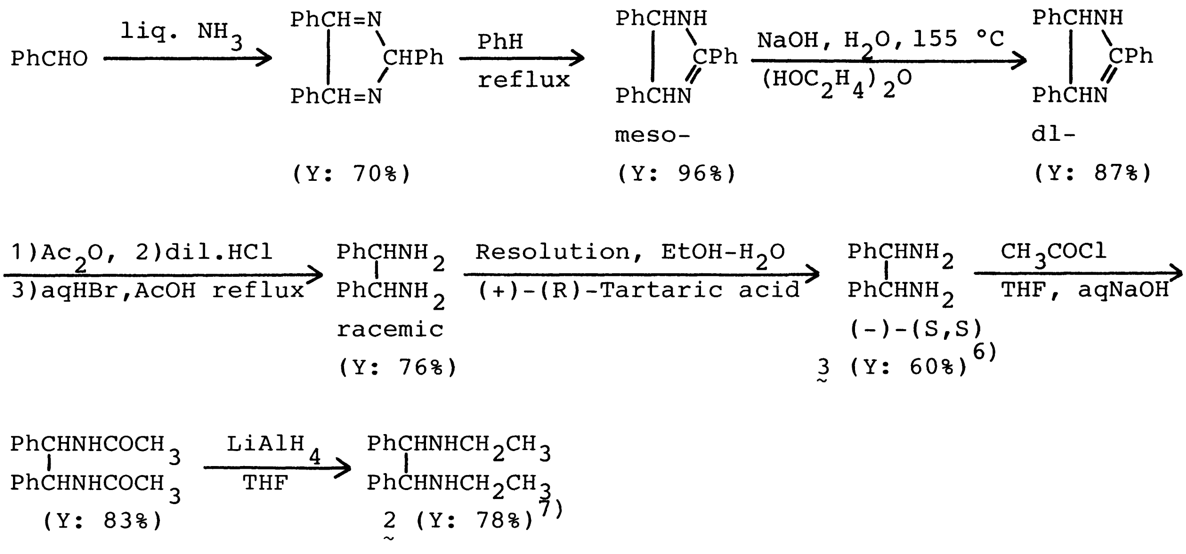


Table 1. Asymmetric reduction of acetophenone with $LiAlH_4$-chiral ligand 1 or 2[a]

No.	Ligand	Achiral alcohol	Chemical yield/%	Enantiomer excess/%
1	1	----	100	2(R)
2	1	EtOH	80	22(S)
3	2	----	90	2(S)
4	2	EtOH	62	2(R)

a) Reaction conditions: Acetophenone/$LiAlH_4$/ligand/(ethanol): 4/10/11/(11), $LiAlH_4$ 1.7 mmol in 16 ml of ether-THF(1/1), -78 °C, 2 h; aging after the addition of ligand and EtOH: 1 h at room temperature respectively.

The yield of 1-phenylethanol was determined by GLC (FFAP 20% on Chromosorb W AW DMCS at 190 °C). The optical yield was also determined by GLC using OV-17 coated lass capillary column at 160 °C as the diastereomeric mixture of esters with (-)-(L)-N-trifluoroacetylalanine.[8] The results in Table 1 show that the effect of added ethanol is significant in the case of the diol 1. Complex hydride reagents of type $LiAlH_n(OR')_{4-n}$ are known to exist in a complicated equilibrium with a variety of disproportionated and aggregated species.[9] It was suggested by Nishizawa and Noyori[1] that ethanol might prevent the disproportionation reactions. In order to obtain some evidence for these speculations, the reaction system was studied by aluminum-27 nuclear magnetic resonance, which were successfully applied to lithium tetrahydroaluminate-tert-butyl alcohol.[10] Figure 1 shows that a proton-coupled quintet spectrum of ^{27}Al of tetrahydroaluminate has a chemical shift of 98 ppm from aqueous aluminum sulfate and a coupling constant of 164 Hz, which is consistent with the previously reported spectrum though the splitting of the signal is not so clear probably due to the association of the species.[10,11] When one molar ratio of ethanol to $LiAlH_4$ is added, a new quadrupole-broadened singlet grows in near 105 ppm, but the quintet signal still detected, which is consistent with the previous reports on the disproportionation reactions.9) When the molar ratio of ethanol / $LiAlH_4$ is 4.5, the signal becomes very weak and hardly detected. When the molar ratio of 1 or 2/$LiAlH_4$ is 1.0, each signal resembles to that in the presence of ethanol. When one molar ratio of ethanol is added to the above 1-$LiAlH_4$ system, only a weak and broad signal is detected at 60 ppm instead of the quintet, which is similar to tert-butyl alcohol/$LiAlH_4$ (3:1) system,10) whereas the quintet does not disapear when one molar ratio of ethanol is added to the 2-$LiAlH_4$ system. These observations indicate that (a) the existence of $LiAlH_4$ species other than the chiral species is the major cause for the low optical yields in Table 1, and (b) the addition of ethanol is effective to exclude the unmodified $LiAlH_4$ species in the former diol system, but not in the latter diamine system, which can explain the difference of effects of added ethanol upon the optical yields between the diol or diamine system in Table 1. Thus, ^{27}Al NMR is a very useful probe for examining alkoxyhydroaluminate species, though the quantative rationalization will need further study.

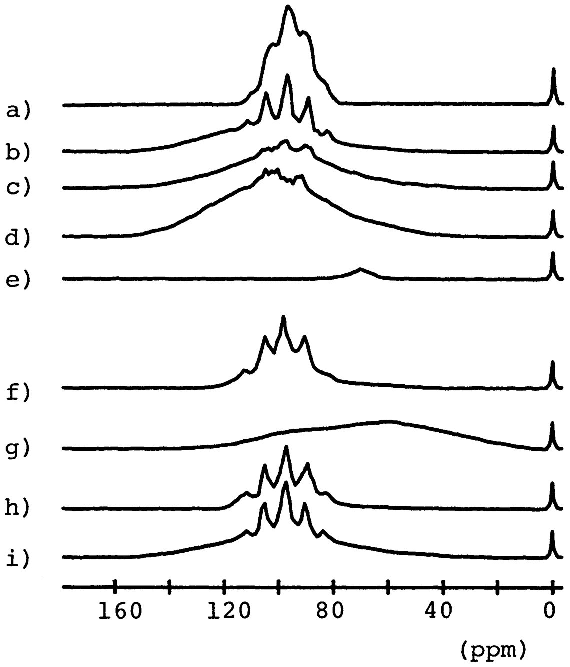


Fig. 1. The 23.46-MHz ^{27}Al spectra of $LiAlH_4$/ligand.12)

a) $LiAlH_4$, b) $LiAlH_4$+EtOH, c) $LiAlH_4$+2EtOH, d) $LiAlH_4$+3EtOH, e) $LiAlH_4$+4.5EtOH, f) $LiAlH_4$ + 1, g) $LiAlH_4$+1+EtOH, h) $LiAlH_4$ +2, i) $LiAlH_4$+2+EtOH. Solvent: THF; Concentration of $LiAlH_4$: 0.34 mol dm^{-3}.

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5) **1** : mp 148.0-149.0 °C; $[\alpha]_D^{22}$ -95.0°(c 1.0, EtOH).

6) **3** : mp 81.7-82.5 °C; $[\alpha]_D^{22}$ -95°(c 0.21, EtOH).

7) **2** : $[\alpha]_D^{23}$ -58°(c 0.91, EtOH).

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12) The ^{27}Al spectra of the solution were obtained on a Hitachi R-90 spectrometer using 8 mm tubes at room temperature. The chemical shifts were measured by suspending a sealed capillary containing a 0.2-0.02 mol dm^{-3} aqueous solution of aluminum sulfate. Amplitude of the signals is scaled by the instrument for each run. Therefore, the amplitudes cannot be related to relative concentrations. Pulse width : 16.0 µs, pulse interval : 1-5 s, No. of acquisition : 100-3600, offset frequency : 23000 Hz, spectrum width : 400 ppm.

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