

ASYMMETRIC REDUCTION OF KETONES WITH A NEW CLASS OF CHIRAL ALUMINUM HYDRIDES.

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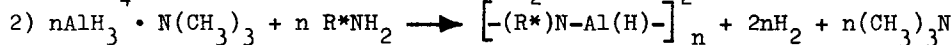
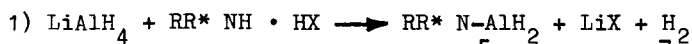
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The asymmetric reduction of prochiral substrates via chiral metallic hydride complexes has been the object of extensive work mostly based on the use of LAH derivatives obtained by reaction with chiral agents such as alcohols, aminoalcohols, monosaccharides<sup>1)</sup>.

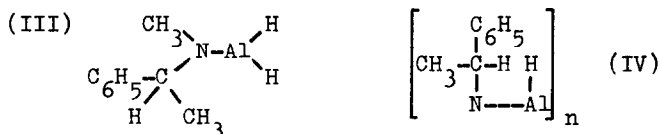
We have prepared and studied a new class of optically active alano derivatives of the following structure



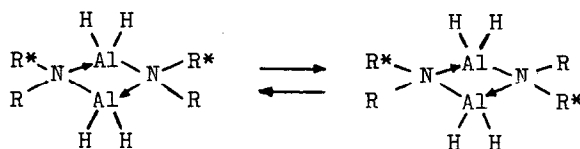
They can easily be synthesized<sup>2,3)</sup> according to the reactions



The remarkable solubility in the different aprotic solvents (THF, ether, benzene, n-hexane), even at temperatures down to -70°C, makes their use in the field of asymmetric reduction very attractive. In this letter we report the preliminary results concerning the synthesis and the properties of



and their behaviour as asymmetric reducing agents of prochiral ketones. The dialkylaminoalane (III), prepared from LAH and N-methyl, N-phenethylamine hydrochloride ( $[\alpha]_D^{23} = -30^\circ$ ,  $c = 5$ , EtOH) has a specific rotation  $\alpha_D^{23} = +27.5$  ( $c = 5$  benzene). Cryoscopic measurements and NMR analysis, both in benzene solution, show the presence of a bridged dimer in cis-trans equilibrium



The poly(*N*-phenethyliminoalane) (IV), obtained by reaction of  $\text{AlH}_3 \cdot \text{N}(\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5)_3$  and *S*(-) phenethylamine, has a polymerization degree  $n \approx 6$ , determined by cryoscopic measurements: the value is in agreement with the reported data for homologous achiral derivatives<sup>3)</sup>. The observed specific rotation is  $[\alpha]_{576}^{24} = +34.5$  ( $c=4.95$ , benzene). Analysis for Al,N,hydridic hydrogen agree in both cases with the theoretical values.

Table 1

Asymmetric ketone reduction with diakylaminoalane (III)

Run n°	R-CO-R'	Solvent	Temp. °C	RCH(OH)R' % yield	Specific rotation $\alpha_{\lambda}^T$ a)	Optical yield %	Absolute config.
1	$\text{C}_6\text{H}_5\text{COCH}_3$	Ether	+21	95	- 4.21	9.5 <sup>b)</sup>	S
2	"	"	0	90	- 5.52	12.5	S
3	"	"	- 8.5	90	- 6.23	14.2	S
4	"	"	-23.5	85	- 7.81	17.7	S
5	"	"	-71	51	-37.55	84.5	S
6	"	toluene	0	95	-12.04	27.4	S
7	"	"	-70	53	-32.35	73.5	S
8	"	THF	0	90	- 1.7	3.85	S
9	"	"	-70	60	-14.6	33	S
10	$\text{C}_6\text{H}_5\text{CH}_2\text{COC}_6\text{H}_5$	Ether	0	90	+ 2.0	3.8 <sup>c)</sup>	S <sup>d)</sup>
11	"	"	-70	50	+32.21	61	S
12	$\text{C}_6\text{H}_5\text{CH}_2\text{COCH}_3$	"	0	90	+ 2.75	8.4 <sup>e)</sup>	S
13	"	"	-70	50	+ 5.06	15.5	S
14	$(\text{CH}_3)_3\text{CCOCH}_3$	"	0	65	+ 0.103	1.3 <sup>f)</sup>	S <sup>g)</sup>
15	"	"	-70	50	+ 1.8	23.3	S

a) All values taken at  $T=25^\circ\text{C}$ ,  $\lambda=589\text{nm}$  unless otherwise stated; b)  $[\alpha]_{\text{D}}^{25} = -44.2^\circ$  (neat); c)  $[\alpha]_{\text{D}}^{25} = +52.8^\circ$  (EtOH)<sup>6)</sup>; d) see ref. 7); e)  $[\alpha]_{546}^{16} = +32.68^\circ$ <sup>8)</sup>; f)  $[\alpha]_{\text{D}}^{20} = +7.84$  (neat)<sup>9)</sup>; g) see ref. 10)

We have attempted the asymmetric reduction of prochiral ketones by examining the influence of some parameters such as temperature, solvent, structure of the substrate, on the optical yield of the reaction. The results are summarized in Tab. 1. The data show a marked dependence of the optical yield from the temperature, in agreement with a kinetic control of the reaction. The high reduction rate prevents any direct kinetic measurement; it is possible however from the known ratios  $c_S/c_R$  of the reduction products at various temperatures to evaluate the enthalpy and entropy differences between the two diastereomeric activated complexes<sup>4)</sup>: for acetophenone reduction by (III) in ether, in the temperature range  $+20^\circ\text{C}$   $-20^\circ\text{C}$  (runs 1-4), we calculate  $\Delta\Delta H_{S-R}^\ddagger = -0.55$  Kcal/mol  $\Delta\Delta S_{S-R}^\ddagger = -1.5$  cal/mol  $^\circ\text{K}$ . The degree of asymmetric induction is also affected by the basicity of the reaction medium: a decrease in optical yield for the reaction of acetophenone, by varying the solvent from toluene (opt. yi.= 27%), to ether (12%), to THF (3.8%), is observed: this can be related to the increasing ability of the solvent to dissociate the bridged dimer, thus leading to a monomeric species of different stereoselectivity. The solvent influence is less evident at low temperatures probably because of the higher stability of the dimeric structure.

The dependence of the optical yield on the nature of the carbonyl substituents is rather complex: steric effects combine with inductive ones and it is difficult to establish which one prevails. We merely observe that the presence of an aromatic group in the ketone to be reduced leads to an increase of the optical yield and that this effect is magnified when the aromatic group is conjugated with the carbonyl group: the same behaviour has already been observed using lithium aluminum chiral alkoxides, and has been ascribed to the "coordination ability" of the aryl group<sup>5)</sup>.

Table 2

Asymmetric reduction of acetophenone with poly(phenetyliminoalane) (IV) in ether

Run n°	Temp. °C	Carbinol yield %	Specific rotation $\alpha_{25}^D$	Optical yield %
1	+35	90	-0.22	0.5
2	0	70	-4.3	10
3	-10	60	-6.08	13.7
4	-22	45-50	-6.65	15

We finally report the first results on the asymmetric reduction of acetophenone with poly(N-phenethyliminoalane) (Tab. 2). Although the reducing agent (IV) is as soluble as the dialkylaminoalane (III) in the above mentioned solvents there is no reduction of acetophenone at temperatures below  $-30^{\circ}$ : it is likely that the reactivity of the Al-H function is considerably reduced by the presence of two bulky groups bound to the same Al atom, the effect being predominant at temperatures below  $-30^{\circ}\text{C}$ . This hypothesis could also explain why the ketone reduction by (III), which is almost quantitative at  $0^{\circ}\text{C}$ , does not proceed over 50% at  $-70^{\circ}\text{C}$  (Table 1): when half of the keto compound has reacted with the geminal di-hydride, the reduced species becomes actually an aluminum-amino, alkoxy, hydride  $\text{HAL}(\text{OR})(\text{NR}_2)$ , and steric hindrance prevents further reaction with the remaining substrate.

#### References

- 1) J.D. Morrison, H.S. Mosher, "Asymmetric Organic Reactions", Prentice Hall Inc., 1971.
- 2) E. Wiberg, E. Amberger, "Hydrides", Elsevier Publishing Co., 1971.
- 3) S. Cucinella, A. Mazzei, W. Marconi, "Inorg. Chim. Acta Revs.", 1970, 51.
- 4) S. Glasstone, K. Laidler, H. Eyring, "Theory of Rate Processes", Mc Graw Hill London, 1941.
- 5) O. Červinka, "Coll. Czech. Chem. Comm.", 1967, 32, 3897.
- 6) V. Gerrard, J. Kenyon, "J. Chem. Soc.", 1928, 2564.
- 7) G. Berti et al., "J. Org. Chem.", 1965, 30, 4091.
- 8) J. Kenyon et al., "J. Chem. Soc.", 1935, 1072.
- 9) R.H. Pickard, J. Kenyon, "J. Chem. Soc.", 1914, 105, 1115.
- 10) Mills and Klyne, "Progr. Stereo-chemistry", London, 1954 p. 177ff.