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Alkyl Metal Asymmetric Reduction. V.[1] Reduction of Alkyl Methyl Ketones by Chiral Organoaluminum Compounds

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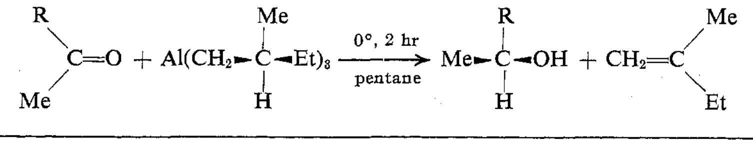
In connection with studies on alkyl metal asymmetric reduction,[1,2] we have extended our investigations on the reaction of some alkyl methyl ketones with optically active 2-methylbutylaluminum derivatives to evaluate the dependence of the stereoselectivity of the reduction on the structure and on the nature of the ketonic substrate employed.

Analogously with previous findings,[2c] (+)-tris[(*S*)-2-methylbutyl]aluminum reacts very fast at 0° in pentane with alkyl methyl ketones too. The reduction affords the corresponding *S* carbinols in satisfactory yields (Table I). The results reported show that the extent of asymmetric induction increases as the steric hindrance to the carbonyl carbon atom is increased, in the order of Et < *i*-Pr < *t*-Bu.[3] The absolute *S* configuration of the predominant enantiomer of the carbinol recovered may be predicted on the basis of the stereochemical model previously proposed.[2c] In fact, even if in this case electronic interactions should not reasonably play an important role, in the preferred transition state of the reduction the ethyl group on the β carbon atom of the aluminum alkyl should be in an anti position with respect to the bulkiest alkyl group of the carbonyl substrate; thus the β hydrogen of the 2-methylbutyl group should be preferentially transferred to the *re* face of the ketone.[2c] This picture satisfactorily explains also the trend of the asymmetric reduction in the series (Table I). In fact, when the effective size of the groups is not a function of their rotational conformations in the transition state,[2c,4] the extent of stereoselectivity should essentially depend on the difference in steric bulk between the alkyl groups substituent to the carbonyl carbon atom.

In our previous paper,[2c] we have pointed out the role of donor solvents in the asymmetric reduction of ketones by optically active organoaluminum compounds. In this context, it was noticeable that (*R*)-*tert*-butylmethylcarbinol was recovered in the reduction of the corresponding ketone by (+)-tris[(*S*)-2-methylbutyl]aluminum diethyl etherate in benzene solution.[5] Since the other chiral groups of the organoaluminum compounds do not affect appreciably the stereoselectivity of the reduction,[2c] this result[5] seemed to indicate that the donor ligand had exerted such a control to afford a carbinol the absolute configuration of which is opposite to that observed in the reduction carried out in the absence of donor ligand (runs 5, 6).

Therefore, to get a deeper insight into the question, we have performed the reduction of *tert*-butyl methyl ketone by (+)-tris[(*S*)-2-methylbutyl]aluminum diethyl etherate at 0° in pentane (run 7, Table II). Although, according to previous findings,[2c] the extent of asymmetric reduction was effectively changed with respect to runs 5 and 6 (Table I), the carbinol recovered had the *S* configuration.

Table I
Asymmetric Reduction of Alkyl Methyl Ketones by (+)-Tris[(*S*)-2-methylbutyl]aluminum[a]



$$\mathrm{R(Me)C{=}O + Al(CH_2\text{—}C(Me)(H)\text{—}Et)_3 \xrightarrow[\text{pentane}]{0^\circ,\ 2\ hr} Me\text{—}C(R)(H)\text{—}OH + CH_2{=}C(Me)(Et)}$$

				Carbinol				
				Optical rotation				
Run	R (registry no.)	Yield, %[b]	Chemical purity, %[c]	α^{25}D, deg, *l* = 1 (neat)	$[\alpha]^{25}$D	$[\alpha]^{25}$D[d]	Optical purity, %	Asymmetric reduction, %[e]
1	Et (4221-99-2)	72.2	~100	+0.51	+0.63	+0.63	4.5[f]	5.3
2	Et	87.0	~100	+0.49	+0.61	+0.61	4.4[f]	5.2
3	*i*-Pr (1517-66-4)	75.2	97	+0.60	+0.74	+0.76	14.2[f]	16.7
4	*i*-Pr	81.5	98	+0.60	+0.74	+0.75	14.0[f]	16.4
5	*t*-Bu (1517-67-5)	36.7[g]	98	+1.02	+1.26	+1.28	16.7[h]	19.6
6	*t*-Bu	66.6	95	+1.00	+1.23	+1.29	16.9[h]	19.8

[a] Optical purity 85.2%. [b] Product recovered by continuous extraction by ether and isolated by distillation. [c] Based on glpc analyses of the products, other impurities being the ketone. [d] Corrected for the per cent purity of the carbinol. [e] Corrected for the minimum optical purity of the organoaluminum compound used. [f] D. Nasipuri and G. Sarkar, *J. Indian Chem. Soc.*, **44**, 165 (1967). [g] The carbinol was not continuously extracted. [h] W. H. Foley, F. J. Welch, E. M. La Combe, and H. S. Mosher, *J. Amer. Chem. Soc.*, **81**, 2779 (1959).

Table II
Asymmetric Reduction of *tert*-Butyl Methyl Ketone by (+)-Tris[(*S*)-2-methylbutyl]aluminum Diethyl Etherate

Run	Solvent	Temp, °C	*S* Carbinol						Asymmetric reduction, %[e]
			Conversion, %[a]	Chemical purity, %[b]	Optical rotation			Optical purity, %[d]	
					$\alpha^{25}\mathrm{D}$, deg, $l = 1$ (neat)	$[\alpha]^{25}\mathrm{D}$	$[\alpha]^{25}\mathrm{D}$[c]		
7[f]	Pentane	0	88	74	+0.31	+0.38	+0.51	11.0[g]	11.5
8[h,i]	Benzene	25	90	~100[j]	+0.86	+1.06	+1.06	13.9	14.2
9[h]	Benzene	80	92	94	+0.55	+0.68	+0.72	9.4	9.6
10[i,k,l]	Benzene	25	63	~100[j]	+0.05 (10.87, EtOH)	+0.46	+0.46	11[m]	~11

[a] Based on glpc analyses of the crude product. [b] Estimated by glpc analyses of the product after redistillation, other impurities being the ketone. [c] Corrected for the per cent purity of the carbinol. [d] W. M. Foley, F. J. Welch, E. M. La Combe, and H. S. Mosher, *J. Amer. Chem. Soc.*, **81**, 2779 (1959). [e] Corrected for the minimum optical purity (o.p.) of the organoaluminum compound. [f] $\mathrm{Al2MB \cdot Et_2O}$, o.p. 95.9% [g] Pure (+)-(*S*)-*tert*-butylmethylcarbinol, $[\alpha]^{25}\mathrm{D}$ +1.30° (neat), o.p. 17.0%, showed $[\alpha]^{25}\mathrm{D}$ +0.79° in the presence of 22% of the corresponding ketone. [h] $\mathrm{Al2MB \cdot Et_2O}$, o.p. 98.0%. [i] According to Kretchmer's procedure (see ref 5). [j] Recovered by preparative glpc. [k] $\mathrm{Al2MB \cdot Et_2O}$, o.p. 94.4%. [l] In the presence of (*S*)-2-methylbutoxyaluminum species (per cent of alkoxide groups 15.9). [m] Pure (+)-(*S*)-*tert*-butylmethylcarbinol, o.p. 16.5%, showed $[\alpha]^{25}\mathrm{D}$ +0.71° (*c* 7.05, EtOH).

As the discrepancy between our result and the result reported in the literature[5] might have arisen from differences in experimental procedures,[6,7] we have carried out the reduction in refluxing benzene[5] (runs 8 and 9, Table II). In addition, we have tested the influence of (*S*)-2-methylbutoxyaluminum species,[8] eventually present in the reaction mixture as oxidation products, on the stereochemistry of the reduction (run 10). In any case *S* carbinol was recovered (Table II). At present we are unable to offer a really satisfactory interpretation about the result reported in the literature.[5]

In conclusion, although the intervention of donor ligands in the reduction controls the extent of stereoselectivity,[2c] at least in the cases investigated the absolute configuration of the carbinol seems to be related only to the structure of the chiral alkyl group bound to the aluminum atom.

Experimental Section[9]

Reduction of Alkyl Methyl Ketones. The following procedure is representative of runs 1–7. A solution of 13.5 mmol of the ketone in 10 ml of anhydrous pentane was added rapidly, under nitrogen, to a solution of 15.0 mmol of the organoaluminum compound in 15 ml of pentane, cooled at 0°, in a flame-dried, two-neck, 100-ml flask fitted with a reflux condenser, a dropping funnel, and a magnetic stirrer. An immediate pale yellow coloration developed and faded quickly. After 2 hr the resulting mixture was cautiously hydrolyzed with dilute sulfuric acid (pH 5) and the organic products were continuously extracted with purified ether. The carbinol was recovered by accurate distillation.

Reduction of *tert*-Butyl Methyl Ketone. Run 8. The ketone (23.1 mmol) in 5 ml of anhydrous benzene was treated with (+)-tris[(*S*)-2-methylbutyl]aluminum diethyl etherate (21.0 mmol), $[\alpha]^{25}\mathrm{D}$ +22.25° (*c* 4.07, pentane),[2c] in 50 ml of benzene according to Kretchmer's procedure.[5] After 2 hr the solvent was removed *in vacuo*, and the resulting mixture was added with ether and hydrolyzed with dilute sulfuric acid. The carbinol recovered by continuous extraction was purified by preparative glpc on 500 × 0.80 cm 20% BDS on Chromosorb W 60–80 mesh columns at 120°.

Run 9. A solution of 14.9 mmol of (+)-tris[(*S*)-2-methylbutyl]aluminum diethyl etherate in 40 ml of anhydrous benzene was added rapidly to a refluxing solution of 16.4 mmol of the ketone in 10 ml of benzene. The solution was maintained at reflux temperature for an additional 2 hr and then worked up as above.

Run 10. A solution of 20.6 mmol of (+)-tris[(*S*)-2-methylbutyl]aluminum diethyl etherate, $[\alpha]^{25}\mathrm{D}$ +21.43° (*c* 4.68, pentane), in 30 ml of dry benzene was cautiously added, at room temperature, with 9.8 mmol of (−)-(*S*)-2-methyl-1-butanol, $[\alpha]^{25}\mathrm{D}$ −5.76° (neat), o.p. 99%,[10] followed by 21.6 mmol of the ketone in 30 ml of benzene. The mixture was refluxed for 2 hr and then worked up in the usual manner. Glpc analysis (200 × 0.30 cm 20% Carbowax 1500 on Chromosorb W 60–80 mesh columns at 60°) showed a carbinol:2-methyl-1-butanol ratio of 1.33. Preparative glpc on 270 × 0.80 cm 20% Carbowax 20M on Chromosorb A 45–60 mesh plus 200 × 0.80 cm Carbowax 1500 on Chromosorb W 60–80 mesh columns at 120° afforded pure (+)-(*S*)-*tert*-butylmethylcarbinol.

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Registry No.—Ethyl methyl ketone, 78-93-3; isopropyl methyl ketone, 563-80-4; *tert*-butyl methyl ketone, 75-97-8; (+)-tris[(*S*)-2-methylbutyl]aluminum, 4023-25-0; (+)-tris[(*S*)-2-methylbutyl]aluminum diethyl etherate, 18902-57-3.

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(9) (+)-Tris[(*S*)-2-methylbutyl]aluminum and (+)-tris[(*S*)-2-methylbutyl]aluminum diethyl etherate, prepared as previously reported,[2c] were carefully redistilled under nitrogen and stored in sealed glass vials. Optical rotations were taken on a Schmidt-Haensch polarimeter with sensitivity of ±0.005°. Glpc analyses were performed on a C. Erba Fractovap Model GT instrument with flame ionization detectors using, unless otherwise indicate, 200 × 0.30 cm 10% BDS on 60–80 mesh Chromosorb W columns in the range 50–70°. Preparative gplc were carried out on a Perkin-Elmer F 21 instrument.

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Synthesis of Fluoroaromatic Amines

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Fluoroaromatic compounds have proven utility in synthetic[2-4] and theoretical[5-7] organic chemistry, and in can-