Tetrahedron Letters No. 44, pp 4135 - 4138, 1971. Pergamon Press. Printed in Great Britain.

OPTICALLY ACTIVE BERYLLIUM AND ALUMINIUM ALKYLS AS NEW ASYMMETRIC REDUCTION AGENTS: ACTION ON ALKYL PHENYL KETONES

G.P.Giacomelli,R.Menicagli and L.Lardicci
Istituto Chimica Organica - Facoltà di Scienze M.F.N.
Università di Pisa (Italy)

(Received in UK 2 September 1971; accepted for publication 1 October 1971)

During the last years asymmetric reductions of ketones to carbinols using optically active Grignard reagents have been widely investigated[1-4]. The results obtained have been often explained on the assumption that the reactions proceed through diastereoisomeric cyclic transition states of different steric and electronic requirements[2,4,5].A recent report on the mechanism of ketone reduction by triisobutylaluminium[6] has encouraged us to investigate the action of optically active organometallic compounds, other than Grignard reagents,on unsymmetrical ketones.

We are hereby reporting the results obtained in the asymmetric reduction of some alkyl phenyl ketones (I) to carbinols (II) by (+)bis-[(R)--2-methylbutyl]-beryllium (III)[7] and (+)tris-[(S)-2-methylbutyl]-aluminium (IV)[7] (Table).The reactions were carried out in pentane solution at 0°,by adding (I) to a corresponding molar amount of the organometallic compound. After 1 hr the reaction mixtures were hydrolyzed; the alkyl phenyl carbinols (II),recovered from the ethereal extracts,were purified by distillation and their purity (98-99 %) was checked by GLC analysis.The yields of recovery were 61-98 % (Table).In each case,the prevalent enantiomer (II) was levorotatory and hence of (S) absolute configuration[1],in agreement with what previously found in the asymmetric reduction of ketones (I) by Grignard reagents from (+)(S)-1-chloro-2-methylbutane[1] and (+)(S)-1-chloro-2-phenylbutane[3].

Approximately the same percentage of asymmetric synthesis* is found in the reductions of (I) by (III) or (IV),at least under the conditions

---

*The minimum optical purity of (II) was evaluated on the basis of the reliable maximum rotations earlier reported[3].

adopted.It is to be noted that the extent of asymmetric reduction is about two times greater with (III) or (IV) than with the corresponding Grignard reagents[1]: however,as the alkyl group in (I) varies through the series,Et, t-Bu,i-Pr,the stereospecificity of the reaction increases accordingly[1] (Figure)(Table).

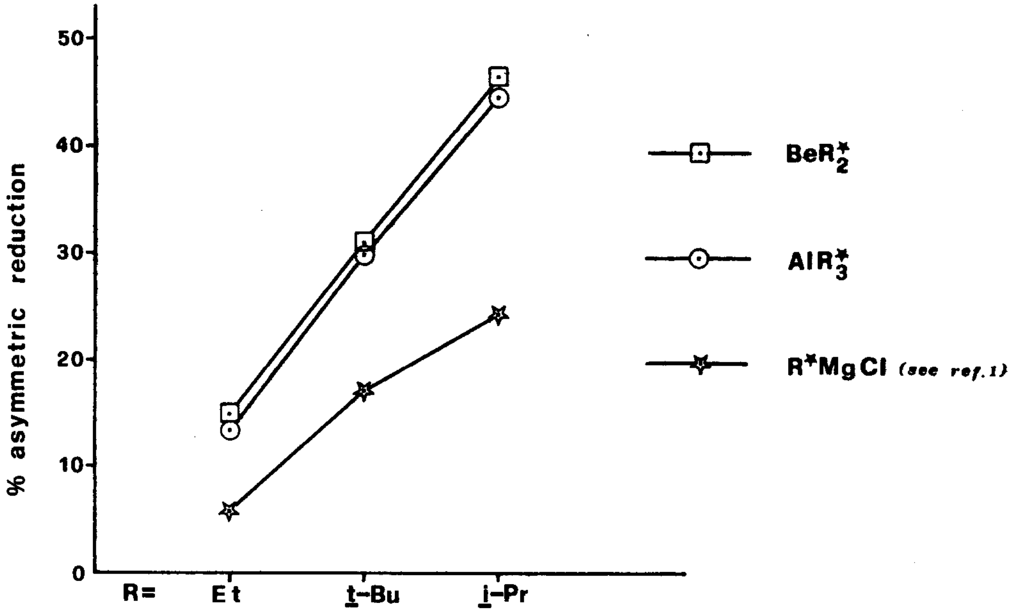

Figure-Asymmetric reduction of ketones (R-CO-Ph) by optically active organometallic compounds MR^*_n [$R^* = Et-\overset{*}{C}H(Me)-CH_2-$].

These asymmetric reduction phenomena support the hypothesis[6] that the reaction involves a transfer of the β-hydrogen of the metal alkyl to the carbonyl carbon through a cyclic six-center transition state rather than an olefin elimination,followed by reduction of the ketone by the metal hydride formed[6].Moreover the results obtained seem to indicate that electronic effects[5],connected with the nature of the organometallic compound,play a significant role in determining the preferred conformations of the transition state,although a detailed rationalization of our data and those previously reported[1-5] appears to be unwarranted at present.

Work is continuing along these lines with further experiments using other carbonyl substrates and organometallic compounds under different reaction conditions.

TABLE

OPTICALLY ACTIVE CARBINOLS FROM REDUCTION OF ALKYL PHENYL KETONES (R-CO-Ph) BY BERYLLIUM AND ALUMINIUM ALKYLS ($M[-CH_2-\overset{*}{C}H(Me)Et]_n$).

M	R	Carbinol (II)						Asymmetric reduction %[d]
		yield %	purity %	$\alpha_D^{25}(l=1)_{expt.}$	c,g/100 ml[a]	$[\alpha]_D^{25}$ [b]	o.p.%[c]	
Be(III)[e]	Et	88.5	97.6	-1.51°	---[f]	- 1.56	5.4	14.8
	i-Pr	97.5	98.6	-0.36°	4.550	- 8.02	16.8	46.2
	t-Bu	90.5	98.4	-0.32°	8.006	- 4.07	11.2	30.8
Al(IV)[g]	Et	75.6	99.4	-2.54°	---[f]	- 2.58	8.9	13.2
	i-Pr	60.6	98.4	-0.71°	5.046	-14.30	30.0	44.4
	t-Bu	82.0	99.3	-0.70°	9.666	- 7.29	20.1	29.8

(a)Ether solvent. (b)Corrected for the % purity of (II). (c)See ref.3. (d)Corrected for the minimum optical purity of the organometallic compound used. (e) $[\alpha]_D^{25}$+14.00 (benzene),o.p. 36.4%. (f)Neat, d_4^{25}0.9915. (g) $[\alpha]_D^{25}$+20.25 (benzene),o.p. 67.5%.

References

1. R.MacLeod,F.J.Welch and H.S.Mosher,J.Amer.Chem.Soc.,82,876 (1960).
2. E.P.Burrows,F.J.Welch and H.S.Mosher,J.Amer.Chem.Soc.,82,880 (1960).
3. J.S.Birtwistle,K.Lee,J.D.Morrison,W.A.Sanderson and H.S.Mosher, J.Org.Chem.,29,37 (1964).
4. J.D.Morrison,D.L.Black and R.W.Ridgway,Tetrahedron Letters,985 (1968).
5. D.Nasipuri,C.K.Ghosh,P.R.Mukherjee and S.Venkataraman,Tetrahedron Letters, 1587 (1971).
6. E.C.Ashby and S.H.Yu,J.Org.Chem.,35,1034 (1970).
7. L.Lardicci,L.Lucarini,P.Palagi and P.Pino,J.Organometal.Chem.,4,341 (1965).