Tetrahedron Letters No. 8, pp 687 - 690, 1972. Pergamon Press. Printed in Great Britain.

ALKYL METAL ASYMMETRIC REDUCTION.II[1].STERIC CONTROL OF A γ-CHIRAL CENTER IN THE REDUCTION OF ACHIRAL KETONES.

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

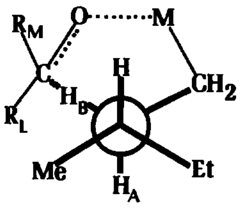
(Received in UK 14 December 1971; accepted for publication 19 January 1972)

The problem of the steric control of a γ-asymmetric center in the Grignard reagents on the reduction of achiral ketones has been previously investigated[2-5].No appreciable asymmetric induction has been found in the reduction of methyl-t.butylketone by the Grignard reagent from (+)(S)-1-chloro-3-methylpentane[2].Contrary to this finding[2] and to the hypothesis[3] that an asymmetric hydrogen transfer occurs only when the chiral center in the Grignard reagent partakes in the six-membered ring transition state[2,3],an asymmetric reduction (25-29%) of phenyl-i.propylketone by the Grignard reagents from (-)(R)-1-chloro-3-phenylbutane and (-)(R)-1-chloro-3-phenylpentane has been recently reported[4].In connection with our experiments on the asymmetric reduction of alkylphenylketones by optically active beryllium and aluminium alkyls[1] we have investigated the effect of a γ-chiral center with respect to the aluminium atom on the asymmetric bias of the reduction of ketones.

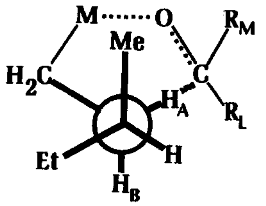
Tris-[(S)-3-methylpentyl]-aluminium[6](I,M=Al/3) was reacted,in pentane solution at 0°,with the corresponding molar amount of the ketone (II)(Table). After 3 hr the reaction mixtures were cautiously hydrolyzed and the products recovered from the ethereal extracts.Appreciable amounts of addition (12-38%) and enolization products (4-17%) were formed together with the carbinols (III) (58-82%) as determined by GLC analysis of the undistilled reaction mixtures. The optical activity of (III) was measured on redistilled samples containing, as impurities,the ketone (II)(4-21%) and the optically active addition product (0-3%).The optical purity of (III) was evaluated by correcting the experimental rotations on the assumption of a linear relationship between the % composition and rotations in the mixtures[7].

In a typical run,reaction of (I,M=Al/3),o.p.82.0%[6],with (II,R=Ph, R_1=i.Pr) gave a 58% yield of (III),o.p.15.3%(Table) and a corresponding amount of (+)(S)-3-methyl-1-pentene (IV),$[\alpha]_D^{25}$+31.9(neat),o.p.84.0%[8*],in addition to a substantial amount of (+)-2,6-dimethyl-3-phenyl-3-octanol (V)(*Anal*.Found:C, 81.60;H,10.95.Calcd.for $C_{16}H_{26}O$:C,81.99;H,11.18),b.p.107°/1 mm,n_D^{25}1.4989, $[\alpha]_D^{25}$+7.6(c=3.410,ether)(structure conforms with mass spectrum).It is to be noted that also the Grignard reagent from (+)(S)-1-bromo-3-methylpentane,o.p. 95.9%[9],reacts with (II,R=Ph,R_1=*i*.Pr) to yield 8% of carbinol (III),o.p.11.0% (Table) and 73% of (V),$[\alpha]_D^{25}$+8.8(c=4.092,ether).In each case,the prevalent enantiomer (III) had (S) absolute configuration[7,10](Table).

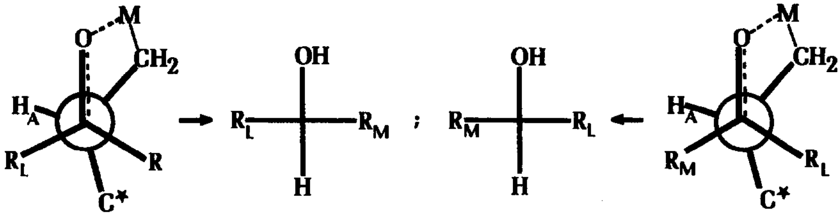
The β-carbon atom in (I),from which hydrogen is transferred,is a new asymmetric center in the "presumably nearly planar",cyclic transition state[4]. Under the hypothesis that the steric interactions play the principal role and may be evaluated from Newman projection formulas[11],viewed in the direction of the bond linking the γ- and the β-carbon atom,only two preferential reacting conformations (**a**)(**b**) are to be considered[**].The conformation (**a**),in which the groups of like relative steric requirements are *anti*,is evidently more stable than (**b**);therefore the hydrogen labelled H_B(pro-R)[5] is transferred preferentially to one or the other enantiotopic faces of the carbonyl group [(**c**)(**d**), viewed along the C···H_B—C axis].The conformation (**c**) presumably represents a lower energy transition state than (**d**);on this basis a predominance of the (S) enantiomer would be expected and this is indeed found (Table).



(a)

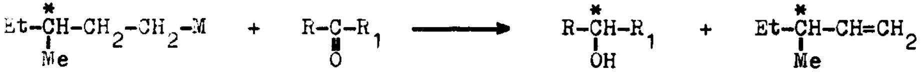


(b)



(c) S R **(d)**

It appears therefore that an asymmetric center in γ-position,as in (I), TABLE



$$\underset{\text{Me}}{\text{Et-}\overset{*}{\text{C}}\text{H}}\text{-CH}_2\text{-CH}_2\text{-M} + \underset{\text{O}}{\text{R-}\overset{}{\text{C}}}\text{-R}_1 \longrightarrow \underset{\text{OH}}{\text{R-}\overset{*}{\text{C}}\text{H}}\text{-R}_1 + \underset{\text{Me}}{\text{Et-}\overset{*}{\text{C}}\text{H}}\text{-CH=CH}_2$$

(I) (II) (III) (IV)

M	(II)		Conditions	(III)					Asymmetric reduction%[d]
	R	R$_1$		yield%[a]	α_D^{25}(l=1)[b]	c,ether	$[\alpha]_D^{25}$ [b]	o.p.%[c]	
Al/3[e]	t.Bu	Me	Normal addn.	82	+0.57°	--[f]	+0.70	9.2	11.2
	Ph	Et	Reverse addn.	63	-2.86°	--[g]	-2.89	10.1	12.3
	Ph	i.Pr	Normal addn.	70	-0.35°	4.930	-7.10	14.9	18.2
	Ph	i.Pr	Normal addn.[h]	58	-0.40°	5.482	-7.29	15.3	18.6
MgBr[i]	Ph	i.Pr	Reverse addn.[l]	8[m]	-0.32°	6.073	-5.27	11.0	11.5

(a) By GLC analysis of undistilled reaction mixtures. (b) Corrected for the % purity of (III). (c) See ref. 7, 10 (d) Corrected for the minimum optical purity of (I). (e) $[\alpha]_D^{25}$ +20.12(neat), o.p. 82.0%. (f) Neat, d_4^{25} 0.810. (g) Neat, d_4^{25} 0.9915. (h) In absence of solvents. (i) From (+)(S)-1-bromo-3-methylpentane, $[\alpha]_D^{25}$ +19.6(neat), o.p. 95.9%. (l) In ether, at 35°. (m) (III) was recovered by preparative GLC.

controls the chirality of the β-carbon atom in the transition state and, consequently, that of the incipient asymmetric carbinol carbon.

REFERENCES AND FOOTNOTES

*The optical purity of (IV) indicates that no racemization of (I) occurs during the reduction process.

**These conclusions are supported by inspection of molecular models.

1.G.P.Giacomelli,R.Menicagli and L.Lardicci,Tetrahedron Letters,4135(1971).
2.H.S.Mosher and E.La Combe,J.Amer.Chem.Soc.,72,4991(1950).
3.E.L.Eliel,Stereochemistry of Carbon Compounds,p.72,McGraw Hill,New York (1962).
4.J.D.Morrison,D.L.Black and R.W.Ridgway,Tetrahedron Letters,985(1968).
5.J.D.Morrison and H.S.Mosher,Asymmetric Organic Reactions,p.198,Prentice Hall,Inc.,Englewood Cliffs,New Jersey (1971).
6.L.Lardicci,P.Salvadori and P.Palagi,Ann.Chim.(Rome),56,1043(1966).
7.H.S.Mosher and E.La Combe,J.Amer.Chem.Soc.,72,3994(1950).
8.L.Lardicci,C.Botteghi and E.Benedetti,J.Org.Chem.,31,1534(1966).
9.P.Salvadori,L.Lardicci and M.Stagi,Gazz.Chim.Ital.,98,1400(1968).
10.R.Mac Leod,F.J.Welch and H.S.Mosher,J.Amer.Chem.Soc.,82,876(1960).
11.D.Nasipuri,C.K.Ghosh,P.R.Mukherjee and S.Venkataraman,Tetrahedron Letters, 1587(1971).