Reduction of Chiral Acyclic Ketones with Hydride-transfer Agents. Semiempirical Analysis of the Observed Stereoselectivity

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(±)-2,2,6,6-Tetramethyl-5-phenylheptan-3-one (**1**), (±)-4,4-dimethyl-1,3-diphenylpentan-1-one (**2**), (±)-2-methyl-1,3-diphenylpropan-1-one (**3**), and (±)-2,3,3-trimethyl-1-phenylbutan-1-one (**4**) have been reduced with lithium tetrahydridoaluminate (LAH), sodium tetrahydridoaluminate (NAH), lithium tri-t-butoxyhydridoaluminate (LTBHA), lithium tetrahydridoborate (LBH), lithium tri-s-butylhydridoborate (LS = lithium selectride) and potassium tri-s-butylhydridoborate (KS = potassium selectride) using different solvents and reaction conditions. For ketones (**1**) and (**2**) some correlations with the observed stereoselectivity have been found. The applicability of a semiempirical scale for the effective size of reagent to the stereochemical analysis of the observed asymmetric induction has been tested.

The stereochemical course of nucleophilic addition to chiral carbonyl compounds has long been studied. Studies of the behaviour of different structural series of carbonyl compounds in concert with different reagents have led to several rationalizations which have proved their usefulness for predicting new results. However, much controversy about the factors controlling the observed asymmetric induction is going on and many questions remain unresolved.

Thus, the approach of the nucleophilic reagent to both prochiral faces of the carbonyl group has been considered to be controlled by steric and/or stereoelectronic factors.[1–20] The balance between these factors will be based on the selection of the transition states involving the easiest access for the reagent (steric control of approach) due to unstabilizing steric factors and the variation of selectivity produced by changes in the hardness of reagent and/or environmental polarity.[13,21–28] The latter will only become important if polar substituents are attached to the carbon atom adjacent to the carbonyl group.

A study of the stereoselectivity of the reduction of (±)-2,2,6,6-tetramethyl-5-phenylheptan-3-one (**1**), (±)-4,4-dimethyl-1,3-diphenylpentan-1-one (**2**), (±)-2-methyl-1,3-diphenylpropan-1-one (**3**), and (±)-2,3,3-trimethyl-1-phenylbutan-1-one (**4**) with different hydride-transfer reagents for several solvents and reaction conditions has been carried out (Table 1).

The results of reduction (**1**)—(**4**) with lithium tetrahydridoaluminate (LAH) in Et_2O at 25 °C have been previously reported.[11,29–33] Ketones (**1**) and (**4**) display high stereoselectivity forming 88% (3*R*5*S*,3*S*5*R*) and 99% (1*R*2*R*,1*S*2*S*) racemate, respectively. However, very low asymmetric induction for ketones (**2**) and (**3**) was reported: 54% (1*R*3*S*,1*S*3*R*) and 55% (1*R*2*S*,1*S*2*R*) racemate, respectively.

The small variations observed for asymmetric induction in reduction of ketones (**2**) and (**3**) precluded the analysis of the stereochemical results. A choice among the transition states has been accomplished through a comparative study between the results for ketones (**2**) and (**3**) and for (**1**) and (**4**). A number of correlations between the observed stereoselectivity in the reduction of ketones (**1**) and (**2**) with some of the variables [type of metal ion in the complex (B and Al), nature of the metallic counter-ion (Li^+, Na^+, K^+), solvent (Et_2O, THF, DME, THF–HMPA 80:20 v/v), addition of Li^+ and Na^+ as common ions, and stoicheiometric addition of the specific crown ether for Na^+] have been made.

The steric requirements of the attacking hydride in each set of conditions have been taken into account in order to establish a semiempirical scale for the effective size of the reagent.

Ketones (**1**) *and* (**2**).—High stereoselectivity in the (3*R*5*S*,3*S*5*R*) isomer for the reduction of ketone (**1**) with LAH in Et_2O at 25 °C has been reported.[29] The direction of asymmetric induction for all conditions used has been conserved (Table 1, runs 1—19; run 20 is an exception). Variations of stereoselectivity have been observed by changing the following conditions:[13,24,34,35] (a) intrinsic size of the complex anion (Table 1; runs 5 and 17; 2 and 16; 7 and 18; 1 and 6; 2 and 7; 3 and 8; 4 and 9; 5 and 10); (b) solvent polarity (Table 1; runs 1, 2, and 5; 6, 7, 10, and 11; 16 and 17); (c) nature of the metallic counter-ion (Table 1; runs 1 and 13; 2 and 14; 18 and 20); (d) addition of a common ion (Table 1; runs 1 and 3; 4 and 5; 6 and 8; 9 and 10; 14 and 15; 18 and 19); and (e) addition of the specific crown ether for Na^+ (Table 1; runs 12 and 14).

Since hydride-transfer reagents can be considered as ate-complexes which exist in solution as several species in equilibrium[34,36,37] (Scheme: A = intimate ion pairs; B = associated ion pairs; C = dissociated ion pairs) depending on the factors quoted above, a semiempirical scale in which the different sets of reagents and conditions has been ordered in terms of the effective volume (V_e) of the attacking hydride may be tentatively established. A scale for the effective volume (V_e) of the hydridoaluminates and hydridoborates can be defined by considering the direction of the stereoselectivity variation observed for ketone (**1**) through an equation of the type $\ln[\%(RS,SR)/\%(RR,SS)] = -V_e + b$. The reference reaction is the stereoselectivity observed for the LAH–DME system (Table 1; run 1). Thus, the sets of reagents and conditions gathered in Table 1 can be arranged according to their V_e values collected in Table 2. For larger V_e values lower stereoselectivities have been observed.

The solvents and the addition of a common ion (Li^+) modified the effective volume for hydride reagents in the opposite direction to that for hydridoaluminates (Table 1 and 2; runs 1—5) and hydridoborates (runs 6—10). This fact can

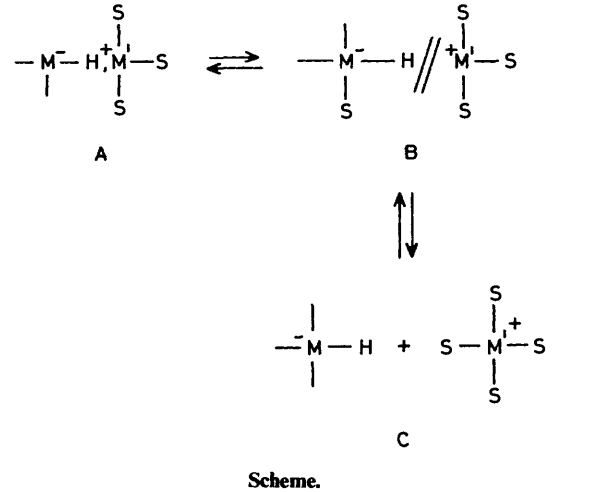
Table 1. Observed stereoselectivity [%(*RS,SR*)/%(*RR,SS*)] in the reduction of acyclic chiral ketones (1)—(4) with complex metal hydrides at 30 °C

Reducing[a] agent	Reaction conditions	Reaction time (h)	%(*RS,SR*)/%(*RR,SS*)[f] Run	Ketone (1)	Run	Ketone (2)	Run	Ketone (3)	Run	Ketone (4)
LAH	DME	0.5	1	6.4 ± 0.6	21	0.82 ± 0.03	41	1.63 ± 0.07	58	0.08 ± 0.01
LAH	THF	0.5	2	6.1 ± 0.5	22	0.92 ± 0.03	42	1.63 ± 0.07	59	0.08 ± 0.01
LAH	DME–$LiClO_4$	0.5	3	5.3 ± 0.4	23	0.85 ± 0.03	43	1.56 ± 0.06	60	0.08 ± 0.01
LAH	Et_2O–$LiClO_4$	0.5	4	4.3 ± 0.3	24	1.17 ± 0.04	44	1.27 ± 0.05	61	0.08 ± 0.01
LAH	Et_2O	0.5	5	4.3 ± 0.3	25	1.17 ± 0.04	45	1.20 ± 0.05	62	0.06 ± 0.01
LBH	DME	3	6	2.2 ± 0.2	26	1.63 ± 0.07	46	1.13 ± 0.04	63	0.06 ± 0.01
LBH	THF	2.5	7	2.1 ± 0.1	27	1.57 ± 0.06	47	1.30 ± 0.05	64	0.06 ± 0.01
LBH	DME–$LiClO_4$	3	8	2.3 ± 0.1	28	1.44 ± 0.06	48	1.04 ± 0.04	65	0.06 ± 0.01
LBH	Et_2O–$LiClO_4$	1	9	2.7 ± 0.1	29	1.17 ± 0.05	49	1.13 ± 0.04	66	0.24 ± 0.02
LBH	Et_2O	1	10	3.0 ± 0.2	30	1.08 ± 0.04	50	1.20 ± 0.05	67	0.28 ± 0.02
LBH	THF–HMPA (80:20)	*b*	11	3.4 ± 0.2	31	0.78 ± 0.03	51	1.25 ± 0.05	68	0.14 ± 0.01
NAH	THF–crown ether	1	12	4.6 ± 0.3	32	0.75 ± 0.03				
NAH	DME	1	13	3.0 ± 0.2	33	0.69 ± 0.03	52	1.27 ± 0.05	69	0.12 ± 0.01
NAH	THF	1	14	3.0 ± 0.2	34	0.69 ± 0.03	53	1.38 ± 0.06	70	0.08 ± 0.01
NAH	THF–$NaClO_4$	1	15	2.9 ± 0.2	35	0.72 ± 0.03				
LTBHA	THF	0.5[c]	16	2.2 ± 0.1	36	1.20 ± 0.05	54	1.04 ± 0.04	71	0.08 ± 0.01
LTBHA	Et_2O	0.5[d]	17	1.25 ± 0.05	37	1.22 ± 0.05	55	1.33 ± 0.06		
LS	THF	2	18	2.2 ± 0.1	38	1.08 ± 0.04	56	1.00 ± 0.04	72	0.00 ± 0.01
LS	THF–$LiClO_4$	2	19	1.82 ± 0.09	39	1.00 ± 0.04			73	0.01 ± 0.01
KS	THF	1[e]	20	0.25 ± 0.02	40	5.7 ± 0.5	57	1.13 ± 0.04	74	0.10 ± 0.01

[a] From the following solutions: 0.13M-LAH–Et_2O; 9 × 10^{-2}M-LBH–Et_2O; 6 × 10^{-2}M-NAH–THF; 3.3 × 10^{-2}M-LTBHA–THF; 1M-LS–THF; 1M-KS–THF. [b] (1) 17 h; (2) 24 h; (3) 10 h; (4) 5 h. [c] For (1) and (2) 20 h. [d] For (1) 20 h and (2) 5 h. [e] For (1) 20 h. [f] Conversions were 100% except for runs 8 (66), 11 (30), 16 (17), 17 (32), 18 (91), 19 (94), 20 (89), 31 (6), 36 (88), 37 (94), 65 (34), 66 (85), and 68 (10%); difference from 100% was starting ketone. The estimation of mixtures of diastereoisomeric alcohols was followed by g.l.c. (runs 1—40 and 58—74) or ^1H n.m.r (runs 41—57) (±3%). Each reaction was repeated two or three times to test the reproducibility of results.

Table 2. Scale of effective volume (V_e) from the reaction ln[%(*RS,SR*)/%(*RR,SS*)] = $-V_e + b$

Run	1	2	3	4	5	6	7	8	9	10
V_e	0.00	0.05	0.19	0.40	0.40	1.07	1.11	1.02	0.86	0.76
Run	11	12	13	14	15	16	17	18	19	20
V_e	0.65	0.34	0.76	0.75	0.81	1.06	1.63	1.06	1.26	3.24



Scheme.

probably be ascribed to a significant difference between the intrinsic volumes of both ate-complexes. Thus, the AlH_4 is a bulky and very polarizable anion which can be highly dissociated in ethereal solutions[36,37] (Scheme: C). The extent of this dissociation can be increased by enlargement of the solvent co-ordination capacity to the metallic counterion (Li^+) in the order Et_2O < THF < DME. Therefore, the effective volume (V_e) of the attacking agent should decrease in the same direction.

Nevertheless, because BH_4^- is a small and slightly polarizable anion[36,37] it has to be considered as an intimate or associated ion pair (A or B, Scheme), independently of solvent polarity. Thus, the effective size of the hydride-transfer reagent can be increased by an enlargement of the solvent co-ordination capacity to the metallic counterion. As expected the smallest steric volume of hydridoborate reagents can be obtained for the dissociation of the ion pairs (Table 1; run 11; THF–HMPA 80:20 v/v). Similar effects can be observed for sodium tetrahydridoaluminate when a specific sodium crown ether is added (Table 1; run 12). In these conditions sodium tetrahydridoaluminate (NAH) is the smallest reagent (Table 1; runs 13—15).

NAH has always yielded smaller stereoselectivity values than LAH. Probably, the former has a larger size due to the higher association of NAH caused by the lower co-ordination ability of the larger Na^+ cation by the solvent molecules.

LAH and lithium tri-t-butoxyhydridoaluminate (LTBHA) display very different values of V_e (Table 2). This behaviour should be ascribed to their quite different intrinsic volumes. Similar results have been obtained when lithium and potassium tri-s-butylhydridoborate (selectrides) (LS and KS) are compared with the related reagent lithium tetrahydridoborate.

The common ion effect has been found to be different for LAH, NAH, LBH, and LS. With LAH–DME an equilibrium displacement towards the species B at the expense of less bulky species C (Scheme) can be assumed (Table 1; runs 1 and 3). A similar effect for the dissociated species of LS in THF can also be assumed (Table 1; runs 18 and 19). This common ion effect is only unimportant with the less dissociated LAH species (Table 1; runs 4 and 5) and the associated LBH species (Table 1; runs 6 and 8; 9 and 10).

Finally, the lowest stereoselectivity has been observed for KS (Table 1; run 20). Intrinsically, the selectride is a very bulky anion whose effective volume will be greatly influenced by the nature of the metallic counterion (Table 1; runs 18 and 20).

Table 3. Multilineal regression analysis of data for ketone (**2**) using the V_e scale $\ln[\%(RS,SR)/\%(RR,SS)] = aV_e + b$

Correlation number	Reducing[a] system	V_e	Slope	Correlation coefficient
1	All conditions (runs 21—40)	0.00—3.24	0.545	0.835
2	LBH (runs 26—31)	0.65—0.76	1.473	0.975
3	LTBHA (runs 36, 37)	1.06—1.63		
	LS (runs 38, 39)	1.06—1.26	0.767	0.970
	KS (run 40)	3.24		
4	LBH (runs 26—31)	0.65—0.76		
	NAH (runs 32—35)	0.34—0.81	0.742	0.936
	KS (run 40)	3.24		
5	LBH (runs 26—31)	0.65—0.76		
	LS (runs 38, 39)	1.06—1.26	0.685	0.936
	KS (run 40)	3.24		
6	LAH (runs 21—25)	0.00—0.40	0.826	0.906
7	LAH (runs 21—25)	0.00—0.40	−0.154	0.245
	NAH (runs 32—35)	0.34—0.81		
8	LAH (runs 21—25)	0.00—0.40	0.498	0.789
	LBH (runs 26—31)	0.65—0.76		

[a] For identity of runs see Table 1.

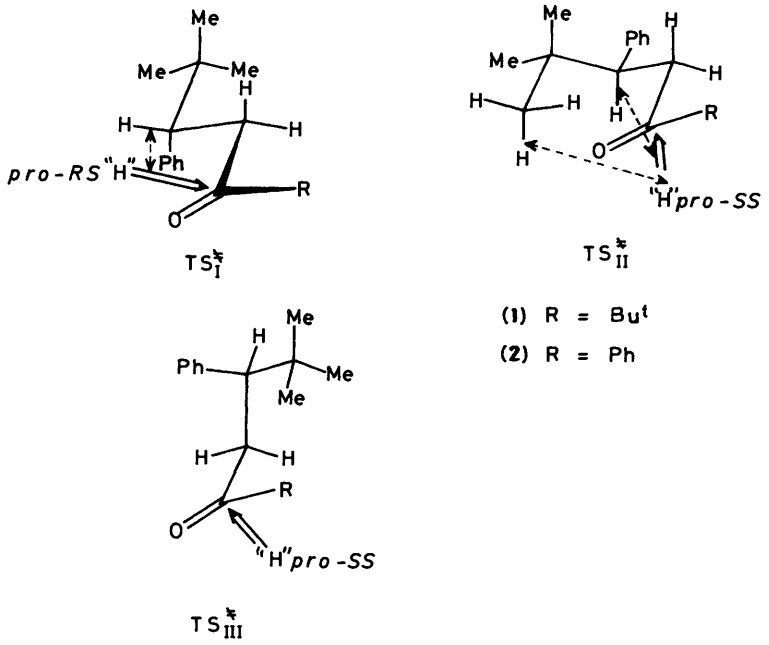


Figure 1.

Complete dissociation of LS in THF occurs but it could be possible that the difficulty of solvation of the bulky K^+ ion confers the nature of a type B associated species on KS (Scheme).

The transition states $TS_I^‡$, $TS_{II}^‡$, and $TS_{III}^‡$ (Figure 1; R = Bu^t) have been proposed to enable discussion on the stereoselectivity observed in the reduction of ketone (**1**) with LAH–Et_2O.[29] These transition states were selected by factors associated with steric control of the approach of the reagent using the empirical model proposed by Karabatsos.[38] The experimental results are explained by the assumption of a selective stabilization of $TS_I^‡$ *versus* $TS_{II}^‡$ and $TS_{III}^‡$. The two latter TS must be destabilized by steric and entropy factors, brought about by the relative position of the two t-butyl groups, so that their participation must be a minimum.

Because of these considerations, an increase in the effective volume of the reagent will lead to an increase of (*RR,SS*) isomer due to lower participation of the $TS_I^‡$. The observed variation may be explained as a consequence of competition between $TS_I^‡$ and $TS_{III}^‡$. An increase in V_e of the reagent causes more participation of $TS_{III}^‡$ *versus* $TS_I^‡$ and $TS_{II}^‡$ due to steric strain between the approaching nucleophile ('H') and the substituents of carbon atom adjacent to the carbonyl group [interactions $('H'–H)_{1,3\text{-p}}$; Figure 1].

The observed asymmetric induction for ketone (**2**) is very low although variation on changing the reaction conditions has been observed (Table 1; runs 21 and 40). Application of the V_e scale (Table 2) to analysis of the results for this ketone shows that the stereoselectivity changes opposite to the way for ketone (**1**). The slopes of the tested correlations show opposite signs. The results of this analysis for various sets of conditions and reagents have been gathered in Table 3.

The linear correlation coefficient is not satisfactory when

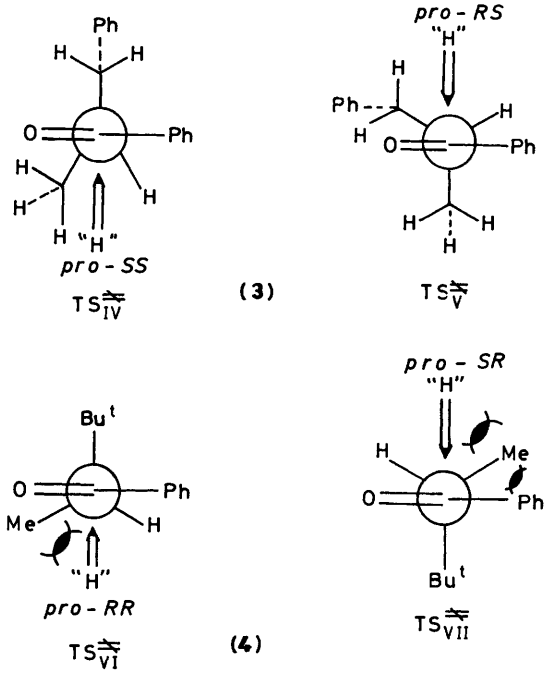


Figure 2.

all the results are taken into account (Table 3; run 1). However, this correlation has statistical significance. When testing the correlation for certain sets of reagents and/or conditions better coefficients are obtained. Therefore, the changes induced on LBH by changing the reaction conditions produce a larger variation of stereoselectivity for ketone (**2**) than for (**1**) (Table 3; correlation 2; slope 1.473). A number of good correlations were obtained when the bulkiest hydrides (Table 3; correlation 3) or reagents with a large association index (LBH, NAH, and KS; Table 3; correlation 4) were selected. A similar result is obtained for the hydridoborates (Table 3; correlation 5). A lower degree of correlation is observed for lithium hydridoaluminates (Table 3; correlation 6). Finally, a correlation is not observed when lithium and sodium hydridoaluminates are considered (Table 3; correlation 7) and when lithium hydridoaluminates and the related hydridoborates are considered together (Table 3; correlation 8). In these cases the absence of correlation can be justified because there is no relation between the degree of association of these reagents.

The reductions of ketones (**1**) and (**2**), whose stereochemical results have been correlated although their slopes show opposite signs, have indicated the participation of a different transition state leading to the *SS*-alcohol for the reduction of ketone (**2**). The formation of this transition state should explain the low asymmetric induction observed with LAH–Et_2O (Table 1; run 25). Therefore, $TS^{\ddagger}_{II}$ must occur instead of $TS^{\ddagger}_{III}$ when V_e is increased to justify its relative destabilization *versus* $TS^{\ddagger}_{I}$. The change of Bu^t in (**1**) to Ph in (**2**) could be the cause of preference of $TS^{\ddagger}_{II}$ over $TS^{\ddagger}_{III}$ for ketone (**2**) because the enthalpy and entropy requirements imposed by Ph were smaller than that of Bu^t (Figure 1).

Ketones (**3**) *and* (**4**).—The observed stereoselectivity for these ketones is collected in Table 1 (runs 41—57 and 58—74, respectively). The high degree of asymmetric induction observed for (**4**) for all reactions tested precluded the development of a similar treatment to that for ketones (**1**) and (**2**).

The stereoselectivity for (**3**) and (**4**) can be explained by the $TS^{\ddagger}_{IV}$, $TS^{\ddagger}_{V}$, $TS^{\ddagger}_{VI}$ and $TS^{\ddagger}_{VII}$ transition states,[32] (Figure 2). These transition states were selected from factors associated with steric control of reagent approach using the empirical model proposed by Felkin.[39] The practically nil influence of the effective volume of the reagent on the observed stereoselectivity can be explained by consideration of these TS.

In agreement with the small variation in the stereoselectivity observed for ketone (**3**) $TS^{\ddagger}_{IV}$ and $Ts^{\ddagger}_{V}$ must occur to a similar extent because they are affected by the variation in V_e of the reagent to the same degree. Similar results were observed for ketone (**4**) because $TS^{\ddagger}_{VI}$ is always more stable.

Experimental

^1H and ^{13}C n.m.r. spectra were recorded on a Varian FT-80A spectrometer (79.542 MHz for ^1H and 20 MHz for ^{13}C). Solutions in $CDCl_3$ (13% and 25% w/v, respectively) at 303 K with Me_4Si as internal reference were used. G.l.c. was carried out on a Perkin-Elmer Sigma-3 instrument with a Sigma 10 data collector.

Ethereal solvents (Et_2O, THF, and DME) and HMPA were purified in the usual manner and distilled over $LiAlH_4$. $LiAlH_4$, $NaAlH_4$, $LiBH_4$, $LiAl[OC(CH_3)_3]_3H$, $LiClO_4$, $NaClO_4$, and dibenzo-18-crown-6 were from Merck and 1M-KS and 1M-LS solutions in THF from Aldrich.

Synthesis.—The ketones (**1**)—(**4**) were prepared and purified as previously reported.[29–32] Characterization was carried out by i.r. and ^1H and ^{13}C n.m.r. ^{13}C Chemical shifts have been reported here for (**2**)—(**4**) by the first time. (±)-2,2,6,6-Tetramethyl-5-phenylheptan-3-one (**1**)[29] and (±)-4,4-dimethyl-1,3-diphenylpentan-1-one (**2**)[30] were obtained by condensation of 4,4-dimethyl-1-phenylpent-1-en-3-one and 1,3-diphenylprop-1-en-2-one with t-butylmagnesium chloride, respectively, in dry diethyl ether. (±)-2-Methyl-1,3-diphenylpropan-1-one (**3**)[31] was prepared by benzylation of the sodium enolate of propiophenone with benzyl chloride. (±)-2,3,3-Trimethyl-1-phenylbutan-1-one (**4**)[32] was also synthetized from propiophenone *via* 2-methyl-3,3-bismethylthio-1-phenylprop-2-en-1-one by addition of lithium dimethylcuprate and subsequent hydrolysis of the intermediate lithium enolate.

^{13}C N.m.r. data are as follows: (**1**), δ 26.33 (2-Me), 28.26 (6-Me), 33.54 (C-6), 37.83 (C-4), 44.18 (C-2), 50.38 (C-5), 126.03 (*p*-C), 127.52 (*m*-C), 129.41 (*o*-C), 142.90 (C-*ipso*), and 213.75 p.p.m. (C-3); (**2**), δ 28.19 (4-Me), 33.91 (C-4), 39.83 (C-2), 51.14 (C-3), 126.16 (*p*-C), 127.62 (*m*-C), 129.42 (*o*-C), 142.45 (C-*ipso*), 127.96 (*o*-C), 128.44 (*m*-C), 132.66 (*p*-C), 137.57 (C-*ipso*), and 199.37 p.p.m. (C-1); (**3**), δ 17.37 (Me), 39.34 (C-3), 42.66 (C-2), 126.14 (*p*-C), 128.21* (*m*-C), 129.03 (*o*-C), 139.87 (C-*ipso*), 128.31* (*o*-C), 128.56 (*m*-C), 132.81 (*p*-C), 136.42 (C-*ipso*), and 203.52 p.p.m. (C-1) (* = interchangeable assignments); (**4**), δ 13.39 (2-Me), 28.00 (3-Me), 33.77 (C-3), 48.21 (C-2), 128.16* (*o*-C), 128.51* (*m*-C), 132.59 (*p*-C), 138.91 (C-*ipso*), and 205.18 p.p.m. (C-1) (* interchangeable assignments).

Preparation and Titration of Complex Metal Hydrides Solutions.—The LAH, NAH, LTBHA, and LBH solutions were prepared as described for LAH solutions[32] from the corresponding complex metal hydride and solvent. The solutions were stored in a dosage burette under an atmosphere of dry nitrogen. Aluminium hydride solutions (LAH, NAH, LTBHA) were titrated by the Felkin method[40] and LBH solution by Lyttle's method.[41] The accuracy of titrations was ±1%. The following solutions were prepared by these procedures: 0.13M-LAH–Et_2O; 6×10^{-2}M-NAH–THF; 3.3×10^{-2}M-LTBHA–THF; 9×10^{-2}M-LBH–Et_2O.

Reduction Reactions.—A four-necked flask provided with a magnetic stirrer, a nitrogen inlet and outlet, a septum for reagent injection, and a connection to the dosage burette of

complex metal hydride solution was used. The flask was evacuated (0.1 Torr) and dry nitrogen passed through. This operation was performed three times. Then, an excess of hydride (2:1) solution under a slow flow of nitrogen was added from a burette or through the septum for LS and KS solutions. At this point, the solvent, if reduction was to be performed in a different solvent from that of the hydride solution, was changed and the stirring was continued until the temperature reached 30 °C. The ketone (50—100 mg) in a minimum amount of solvent (2—3 ml) was injected. The mixture was stirred for a time t_R (see Table 1) at 30 °C. The solution was hydrolysed with a saturated solution of NaCl and the aqueous phase was extracted with Et_2O (3 × 50 ml). The ethereal extracts were washed with a saturated solution of NaCl and dried ($MgSO_4$). Hydrolysis for reductions with LS and KS was achieved with a 3M solution of NaOH (1 ml) and H_2O_2 (5 ml of 30% H_2O_2). The aqueous phase was saturated with K_2CO_3 and extracted with several portions of Et_2O. The solvent was eliminated *in vacuo*.

Reactions in the presence of $LiClO_4$, $NaClO_4$ (molar ratio ketone–salt 1:1.15), or dibenzo-18-crown-6 (molar ratio hydride–crown ether 1:1) were carried out with the above procedure. The salt or crown ether were placed in the flask and dried *in vacuo* before adding the hydride solution.

The reaction products were analysed by g.l.c., i.r., and ^1H n.m.r. Conversion and reaction times of reductions have been collected in Table 1. The stereochemistry of the products was determined for the methods described below.

Assignment of Relative Configurations.—The assignment of relative configurations (*RR,SS*) and (*RS,SR*) to diastereoisomeric racemates, arbitrarily denominated α and β, of the alcohols obtained in the reductions of ketones (**1**)—(**4**) was previously reported: (±)-2,2,6,6-tetramethyl-5-phenylheptan-3-ol (**1a**)[42] α = (3*R*5*S*,3*S*5*R*), and β = (3*R*5*R*,3*S*5*S*); (±)-4,4-dimethyl-1,3-diphenylpentan-1-ol (**2a**)[43] α = (1*R*3*R*,1*S*3*S*) and β = (1*R*3*S*,1*S*3*R*); (±)-2-methyl-1,3-diphenylpropan-1-ol (**3a**)[44] α = (1*R*2*R*,1*S*2*S*) and β = (1*R*2*S*,1*S*2*R*); (±)-2,3,3-trimethyl-1-phenylbutan-1-ol (**4a**)[45] α = (1*R*2*R*,1*S*2*S*) and β = (1*R*2*S*,1*S*2*R*).

Analysis of the Mixtures of Diastereoisomeric Alcohols (**1a**)—(**4a**).—Two methods, ^1H n.m.r. and g.l.c., were followed to obtain the composition of the reaction mixtures (error ±3%). For 2-methyl-1,3-diphenylpropan-1-ol (**3a**) this was carried out by ^1H n.m.r. using as key signals those for CH_3 and 1-H which appear as doublets at different chemical shifts in each diastereoisomer: α-isomer, δ 0.65 (CH_3) and 4.42 (1-H); β-isomer, δ 0.82 (CH_3) and 4.52 (1-H). Signals, appropriately expanded, were repeatedly integrated.

For other cases analysis was achieved by g.l.c., using the following conditions: 2,2,6,6-tetramethyl-5-phenylheptan-3-ol (**1a**), 10% BDS on Chromosorb W-AW-DMCS, length 0.90 m; ø ¼ in; column temperature 115 °C; gas flow (N_2) 56 ml min^{-1}; retention times τ_α 43.2 and τ_β 50.6 min; 4,4-dimethyl-1,3-diphenylpentan-1-ol (**2a**), 10% BDS on Chromosorb W-AW-DMCS; length 0.90 m; ø ¼ in; column temperature 170 °C; gas flow (N_2) 60 ml min^{-1}; retention times τ_α 65.6 and τ_β 73.9 min; 2,3,3-trimethyl-1-phenylbutan-1-ol (**4a**), 12% Carbowax-20M on Chromosorb W-AW-DMCS; length 2 m; ø ⅛ in; column temperature 155 °C; gas flow (N_2) 20 ml min^{-1}; retention times τ_α 36.5 and τ_β 40.1 min.

The results are collected in Table 1 and are given as %(*RS,SR*)/%(*RR,SS*).

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