Alkyl Metal Asymmetric Reduction. Part IV.[1] Reduction of Isopropyl Phenyl Ketone by Optically Active Dialkylzinc Compounds: Dependence of Stereoselectivity on the Distance of the Chiral Centre from the Metal Atom †

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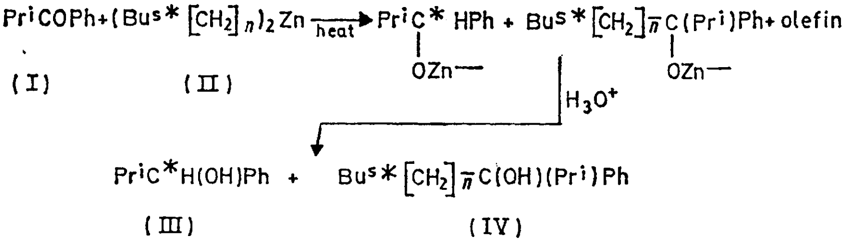
The reaction between isopropyl phenyl ketone and optically active dialkylzinc compounds of general formula $(Bu^{s*}[CH_2]_n)_2Zn$ (n = 1, 2, or 3) leads to optically active 2-methyl-1-phenylpropan-1-ol, and the stereoselectivity of the reduction process is dependent on the distance of the chiral centre from the metal atom. The results are rationalized in terms of conformational requirements of the non-reacting groups which, determining the preferential transfer of one of the two β-hydrogen atoms to the metal atom, should control the stereoelectronic interactions among the reacting groups in the diastereoisomeric transition states.

ORGANOMETALLIC compounds of second and third group elements are often able to reduce carbonyl substrates to the corresponding carbinols: when the organometallic compound is optically active the resulting carbinols are also optically active.[1-5] These reactions are usually interpreted in terms of hydride transfer from the β-carbon atom with respect to the metal atom to the carbonyl carbon atom through diastereoisomeric six-membered cyclic transition states.[1-5] Asymmetric reduction studies have been generally carried out by employing organometallic compounds with the asymmetric carbon atom in the β-position with respect to the metal atom.[1,2,4] However it was recently established that asymmetric reduction of prochiral ketones by chiral Grignard reagents,[3-5] aluminium alkyls,[5] or halogenomagnesium alkoxides[6] is possible even when the carbon atom from which hydrogen transfer occurs is not formally asymmetric.

In order to gain further information about this problem, in connection with a more systematic investigation on the dynamics and the stereochemistry of the reduction of prochiral ketones by dialkylzinc compounds,[7] we have investigated the influence of the distance of the asymmetric centre from metal atom on the stereoselectivity of the ketone reduction. We now report the results obtained by reducing isopropyl phenyl ketone (I) with (+)-bis-[(*S*)-2-methylbutyl]zinc (II; $n = 1$),[8] (+)-bis-[(*S*)-3-methylpentyl]zinc (II; $n = 2$),[8] and (+)-bis-[(*S*)-4-methylhexyl]zinc (II; $n = 3$).[8]

The experiments were carried out at 86·5°, in the absence of solvent, by treating the ketone (I) with a 10% excess of the dialkylzinc compound (II). The reactions proceeded with high conversions (Table) yielding essentially the reduction product (III): however, when (II; $n = 2$) or (II; $n = 3$) was used, g.l.c. analyses of the crude products revealed the presence of small amounts (1—3%) of the addition product (IV). Also, the reaction rate seems to be dependent on the structure of (II): compound (II; $n = 2$) reduced (I) with the lowest conversion. During the reaction the olefin corresponding to the alkyl group bound to the zinc atom is distilled off and can be collected in quantitative amount. The recovery of (+)-(*S*)-3-methylpent-1-ene and (—)-(*S*)-4-methylhex-1-ene of optical purity[9,10] corresponding to that of the starting dialkylzinc (II) confirms that the reduction process, which involves the hydrogen atoms β to the metal atom, occurs without racemization.[5] In all the cases the carbinol (III) recovered was optically active and of absolute *S*-configuration[11] (Table). Its optical activity was measured



$$\mathrm{Pr^iCOPh + (Bu^{s*}[CH_2]_n)_2Zn \xrightarrow[heat]{} Pr^i\underset{\substack{|\\ OZn-}}{C^*}HPh + Bu^{s*}[CH_2]_n\underset{\substack{|\\ OZn-}}{C}(Pr^i)Ph + olefin}$$

(I) (II)

$$\xrightarrow{H_3O^+}$$

$$\mathrm{Pr^iC^*H(OH)Ph + Bu^{s*}[CH_2]_nC(OH)(Pr^i)Ph}$$

(III) (IV)

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[3] J. D. Morrison, D. L. Black, and R. W. Ridgway, *Tetrahedron Letters*, 1968, 985; J. D. Morrison and R. W. Ridgway, *J. Amer. Chem. Soc.*, 1969, **91**, 4601.

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[5] L. Lardicci, G. P. Giacomelli, and R. Menicagli, *Tetrahedron Letters*, 1972, 687.

[6] J. D. Morrison and R. W. Ridgway, 161st A.C.S. National Meeting, Los Angeles, California, March—April 1971; Abstracts, 151 ORGN.

[7] L. Lardicci, unpublished data.

[8] L. Lardicci and L. Lucarini, *Ann. Chim.* (*Italy*), 1964, **54**, 1233.

[9] P. Pino, L. Lardicci, and L. Centoni, *J. Org. Chem.*, 1959, **24**, 1399.

[10] P. Pino, L. Lardicci, and L. Centoni, *Gazzetta*, 1961, **91**, 428.

[11] J. S. Birtwistle, K. Lee, J. D. Morrison, W. A. Sanderson, and H. S. Mosher, *J. Org. Chem.*, 1964, **29**, 37.

on redistilled samples containing the unchanged ketone too, and therefore the evaluation of the enantiomeric excess in the carbinol was performed on the basis of optical rotations of ethereal solutions of (III) of known optical purity, and containing weighed amounts of (I). The data obtained (Table) show that the reduction is a stereoselective process in all the cases we have investigated and that the extent of asymmetric induction is related to the distance of the chiral centre from the metal atom.

(−)-(*S*)-2-Methyl-1-phenylpropan-1-ol (III) from reduction of the corresponding ketone by optically active dialkylzinc compounds [a]

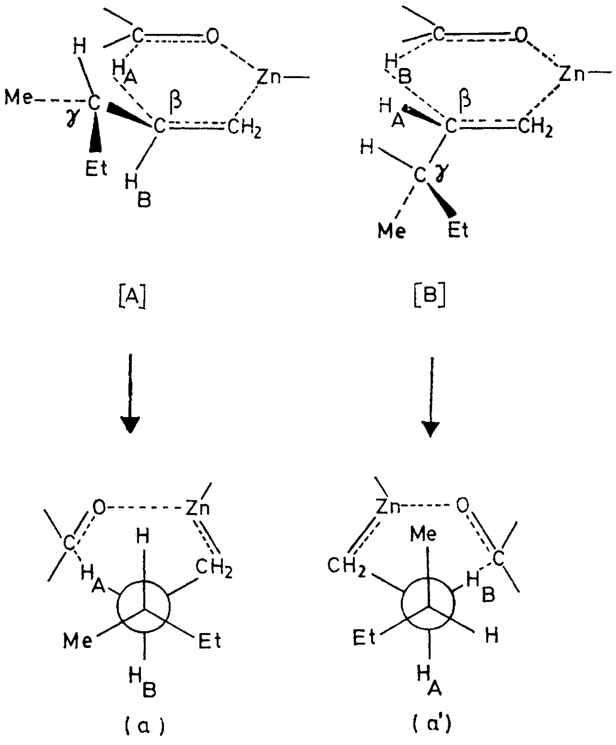
		Yields (%) [b]		Carbinol (III) recovered				
n	Conversion [b] (%)	(III)	(IV)	α_D^{25} (l = 1) (°)	*c* [c] (in Et_2O)	$[\alpha]_D^{25}$	O.p.[d,e] (%)	Asymmetric reduction [f] (%)
1 [g]	89	100		−0·43	5·94	−7·24	15·2	15·5
	87	100		−0·52	7·20	−7·22	15·2	15·5
2 [h]	75	97	3	−0·40	9·03	−4·43	9·3	9·7
	76	96	4	−0·45	10·55	−4·26	8·9	9·3
3 [h]	95	99	1	−0·17	15·00	−1·13	2·4	2·5
	92	99	1	−0·15	11·60	−1·29	2·7	2·8

[a] At 86·5 ± 0·3° for 24 h. [b] Determined by g.l.c. analysis of the crude products. [c] Evaluated from g.l.c. analysis. [d] Optical purity; see Experimental section. [e] See ref. 11. [f] Corrected for the minimum optical purity of the dialkylzinc compound used. [g] O.p. 98·2%. [h] O.p. 95·7%.

In view of previous suggestions,[12] and on the basis of mechanisms proposed for the reduction of ketones by other organometallic compounds,[1-5] the reaction should proceed, even in this case,[7] through a six-membered cyclic transition state in which the hydrogen atom β to the zinc atom is transferred to the carbonyl carbon atom. On this basis the stereoselectivity of the reduction by (II; $n = 1$) and the absolute *S*-configuration of (III) recovered are to be related to the differences in free energy of the diastereoisomeric transition states, in connection with the various stereoelectronic interactions among the groups attached to the β-carbon atom of (II; $n = 1$) and to the carbonyl group of (I).[1,2,4]

The low but definite asymmetric induction observed in the reduction of (I) by (II; $n = 2$) and (II; $n = 3$) shows that steric and electronic interactions play a significant role even in these cases. These data seem to indicate that, in considering transition states for the reduction of ketones by optically active organometallic compounds,[1-5] two factors need to be taken into account, *viz.* the conformational requirements of the groups directly involved in the reaction, and the conformational requirements of the neighbouring non-reacting groups, which should determine a preferential migration of one or the other hydrogen atom (H_A or H_B) in the β-position with respect to the metal atom.

On such a basis, for the transition states [A] and [B] which require the transfer of H_A (*pro*-S) and H_B (*pro*-R) of (II; $n = 2$), respectively, all the possible conformations along the C_γ–C_β bond, which may be rationalized in terms of Newman's projections, are to be considered. If we take into account only steric interactions,[2] on the basis of simple conformational criteria [13] the conformations (a) and (a′) (Scheme 1), in which the ethyl group and the substituent groups on the carbonyl carbon atom of (I) are opposite, appear to be the most stable: (a) however shows lower steric interactions than (a′), since all the groups of like steric bulk are in *anti*-positions.[13] We conclude therefore that, in the case of the reduction of (I) by (II; $n = 2$), the transfer of H_A (*pro*-S) to the *si*- or to the *re*-face of (I) [14] is favoured in comparison with the transfer of H_B. Therefore the absolute configuration of the prevalent enantiomer in (III) should depend on this preferential migration, in relation to the stereoelectronic interactions among the groups directly involved in the transition states of the reduction.



SCHEME 1

On the basis both of steric and electronic factors,[1,15] and considering the most stable reacting conformations, in which H_A is transferred to the *re*-face (b) or to the *si*-face (b′) of the carbonyl compound, rationalized in

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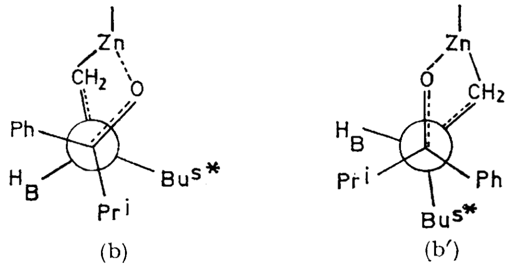
[12] G. E. Coates and D. Ridley, *J. Chem. Soc.* (*A*), 1966, 1064.

[13] E. L. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, p. 138.

[14] K. R. Hanson, *J. Amer. Chem. Soc.*, 1966, **88**, 2731.

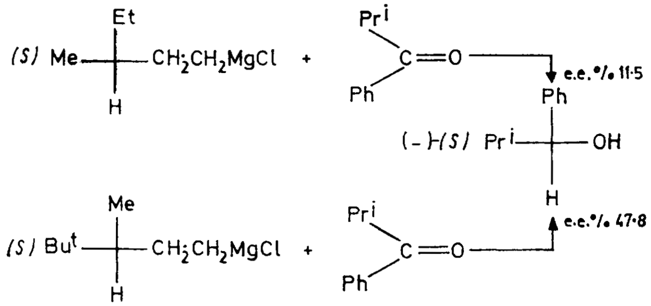
[15] D. Nasipuri, C. K. Ghosh, P. R. Mukherjee, and S. Venkataraman, *Tetrahedron Letters*, 1971, 1587.

terms of Newman-type projections viewed along the $C \cdots H_A$–C_β axis[1] (Scheme 2), it appears that the conformation (b) leading to (*S*)-carbinol represents a lower energy transition state than (b′), since in (b) the bulkiest groups, *i.e.* the phenyl group of the ketone and the alkyl group of (II), are in a quasi-*anti*-position. The *S*-enantiomer of (III) would thus be formed prevalently, in agreement with the experimental findings (Table).



SCHEME 2

On this basis, if the preferential transfer of the one or the other β-hydrogen atom is effectively due to the difference between their chiral environments,[3] it would be expected that the extent of asymmetric induction in the reduction of prochiral ketones by optically active γ-branched organometallic compounds would be enhanced by the presence, on the chiral γ-carbon atom, of groups of very different steric bulk. The results obtained in the reduction of (I) by the Grignard reagents from (+)-(*S*)-1-chloro-3-methylpentane (IV)[5] and (−)-(*S*)-1-chloro-3,4,4-trimethylpentane (V) (Scheme 3) seem to corroborate these predictions, under the hypothesis that the transition states for the hydrogen transfer are similar for Grignard reactions and for dialkylzinc reductions. In fact in (V) the chiral environments of the two β-hydrogen atoms are very different and consequently the stereoselectivity of the reduction by (V) is much higher than for reduction by (IV).

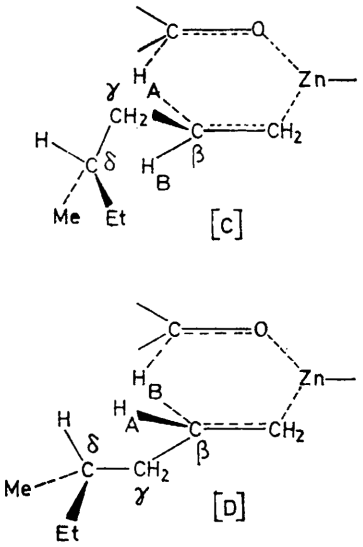


SCHEME 3

e.e. % is the percentage excess of enantiomer over racemate

In compound (II; $n = 3$) the asymmetric carbon atom is more distant than in (II; $n = 2$) from the reacting groups (Scheme 4). In this case it seems reasonable to predict that, owing to the greater distance of the asymmetric centre from the β-carbon atom, the stereoselectivity of the reduction would drop substantially. Nevertheless, as confirmed by inspection of molecular models, taking into account the conformations along both the C_γ–C_β and the C_δ–C_γ bonds, H_A (*pro*-S) should be preferentially transferred and the *S*-enantiomer of (III) should be prevalent even when (II; $n = 3$) is used. The experimental data (Table) effectively confirm this prediction.

In conclusion, the overall results show that optically active dialkylzinc compounds (II) are able to effect asymmetric reduction of prochiral ketones and that the stereoselectivity of the reduction is strictly dependent on the distance of the chiral centre from the metal atom. Further evidence that the essential feature of this type of stereoselective reduction is the difference in chiral environments of the hydrogen atoms available for transfer to the carbonyl carbon atom of the ketone[16] is thus obtained.



SCHEME 4

EXPERIMENTAL

G.l.c. analyses were performed on a C. Erba Fractovap model GT instrument, with flame ionization detectors [200 × 0·30 cm columns packed with 10% butanediol succinate (BDS) on 60—80 mesh Chromosorb W, at 160°]. All rotations were taken on a Schmidt–Haensch polarimeter (sensitivity ±0·005°) for solutions in 1 dm tubes.

Materials.—Isopropyl phenyl ketone (I) was a commercial product (Fluka A.G. Co., Buchs) and was purified by way of its semicarbazone.[17] The dialkylzinc compounds (II) were prepared as previously described,[8] carefully distilled under nitrogen, and stored in sealed glass vials in weighed amounts. All the reactions were carried out in a dry, purified nitrogen atmosphere.

Asymmetric Reduction of Isopropyl Phenyl Ketone (I).—(a) *With* (+)-*bis*-[(S)-2-*methylbutyl*]*zinc* (II; $n = 1$). To a flame-dried flask connected with a liquid-air trap was added compound (II; $n = 1$) (2·453 g, 11·8 mmol) {b.p. 49° at 0·6 mmHg, $[\alpha]_D^{25}$ +9·91 (neat)},[8] followed by the ketone (I) (1·611 g, 10·8 mmol). The flask was then placed for 24 h in an oil-bath maintained at 86·5 ± 0·3°. During the reaction, the liquid-air trap collected a low boiling material (0·675 g), which decolourized a solution of bromine

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[17] C. Djerassi and L. E. Geller, *J. Amer. Chem. Soc.*, 1959, **81**, 2789.

in carbon tetrachloride and was shown to contain 97% of 2-methylbut-1-ene, identified from its g.l.c. retention time (100 m capillary column packed with 10% Squalane on 60—80 mesh Chromosorb W, at 35°). The mixture was then cooled to 0°, diluted with anhydrous diethyl ether (20 ml) and cautiously hydrolysed with dilute sulphuric acid (pH 5). The solvent was then removed and the crude product, containing only the carbinol (III) and the residual ketone, was distilled to yield (−)-(*S*)-(III) (1·359 g, 89·3% pure), b.p. 102° at 18 mmHg (Table).

An ethereal solution containing 6·570 g per 100 ml of (−)-(*S*)-(III) {$[\alpha]_D^{25}$ −16·64 (*c* 5·48 in Et_2O), optical purity 34·9%}[11] and 0·982 g per 100 ml of (I) showed α_D^{25} (*l* 1) −1·09°, $[\alpha]_D^{25}$ −16·59 [ether–(I)].

(b) *With* (+)-*bis*-[(S)-3-*methylpentyl*]*zinc* (II; *n* = 2). To compound (II; *n* = 2) (3·284 g, 13·9 mmol) {b.p. 65° at 0·1 mmHg, $[\alpha]_D^{25}$ +7·87 (neat)}[8] was added the ketone (I) (1·857 g, 12·5 mmol). The mixture was then worked up as in (a).* G.l.c. analysis of the crude product indicated the presence of residual (I), of the carbinol (III), and of a compound with retention time the same as that of authentic 2,6-dimethyl-3-phenyloctan-3-ol (IV; *n* = 2).[5] By careful distillation (−)-(*S*)-(III) (0·980 g, 71·1% pure) was recovered (Table).

An ethereal solution containing 11·31 g per 100 ml of (−)-(*S*)-(III) {$[\alpha]_D^{25}$ −16·64 (*c* 5·48 in Et_2O)} and 4·62 g per 100 ml of (I) had α_D^{25} (*l* 1) −1·88°, $[\alpha]_D^{25}$ −16·62 [ether–(I)].

(c) *With* (+)-*bis*-[(S)-4-*methylhexyl*]*zinc* (II; *n* = 3). Similarly compound (II; *n* = 3) (3·334 g, 12·6 mmol) {b.p. 81° at 0·07 mmHg, $[\alpha]_D^{25}$ +14·71 (neat)}[8] and the ketone (I) (1·687 g, 11·4 mmol) were heated at 86·5 ± 0·3° for 24 h. The crude product † contained the carbinol (III), together with unchanged (I) and <1% of a compound not identified [presumably 2,7-dimethyl-3-phenylnonan-3-ol (IV; *n* = 3)]. This mixture was carefully distilled to give (−)-(*S*)-(III) (0·721 g, 93·4% pure) (Table).

(d) *With* (S)-3,4,4-*trimethylpentylmagnesium chloride*. To an ethereal solution of the Grignard reagent from (−)-(*S*)-1-chloro-3,4,4-trimethylpentane (2·592 g, 17·7 mmol) {n_D^{25} 1·4347, $[\alpha]_D^{25}$ −56·08 (neat), optical purity 84·1%}[18] the ketone (I) (2·094 g, 14·1 mmol) in anhydrous ether (10 ml) was added dropwise. The mixture was refluxed for 2 h, then hydrolysed with dilute sulphuric acid and extracted with ether. G.l.c. analysis of the crude product showed the presence of the carbinol (III) (8%) and of the addition product (92%). This mixture was carefully fractionated to give (−)-2,6,7,7-tetramethyl-3-phenyloctan-3-ol (2·717 g), b.p. 112° at 0·5 mmHg, n_D^{25} 1·4951, $[\alpha]_D^{25}$ −30·8 (*c* 8·50 in Et_2O) (Found: C, 82·5; H, 11·7; O, 5·8. $C_{18}H_{30}O$ requires C, 82·4; H, 11·5; O, 6·1%), and a sample (1·048 g) containing (III). This fraction was separated by preparative g.l.c. on a 180 × 0·8 cm column, filled with 20% BDS on 45—60 mesh Chromosorb W, at 160° (Perkin-Elmer F 21 instrument) to yield (−)-(*S*)-(III) [0·167 g, containing 2·5% of (I)], α_D^{25} (*l* 1) −1·04° (*c* 5·56 in Et_2O), $[\alpha]_D^{25}$ −19·19 [*c* 5·42 in ether–(I)].

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* Low-boiling material (0·775 g), which distilled off during the reaction, was identified by g.l.c. analysis (200 × 0·3 cm columns packed with 20% silver nitrate–ethylene glycol on 60—80 mesh Chromosorb W, at 30°) as (+)-(*S*)-3-methylpent-1-ene, b.p. 54°, n_D^{25} 1·3815, $[\alpha]_D^{25}$ +36·07.[9]

† G.l.c. analysis of the ethereal extracts revealed the presence of 4-methylhex-1-ene, identified from its g.l.c. retention time on 200 × 0·3 cm columns packed with 20% silver nitrate–ethylene glycol on 60—80 mesh Chromosorb W, at 40°. The olefin, recovered (0·520 g) from its dibromide, showed n_D^{25} 1·3978, $[\alpha]_D^{25}$ −2·89.[10]

[18] A. M. Caporusso, G. P. Giacomelli, and L. Lardicci, *Atti Soc. Toscana Sci Nat.* (*Pisa*), 1973, A**80**, 40.