Alkyl Metal Asymmetric Reduction. Part VIII.[1] Stereoselectivity of the Reduction of Alkyl Phenyl Ketones by Optically Active Aliphatic Grignard Reagents

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The reactions between alkyl phenyl ketones and optically active aliphatic Grignard reagents, containing groups of different steric requirements on the chiral carbon atom, have been investigated. Both reduction and addition products were formed, their relative amounts being dependent on the structure of both the ketone and the Grignard reagent. In all cases, optically active carbinols were recovered, whatever the distance of the asymmetric carbon atom from the magnesium atom. The factors controlling the course of the reaction and its stereoselectivity are discussed.

OPTICALLY active Grignard reagents from 1-chloro-2-phenylalkanes and from 1-halogeno-2-methylbutane are known to accomplish asymmetric reductions of prochiral carbonyl compounds.[2] The asymmetric bias of such reactions has been rationalized on the basis of six-membered planar diastereoisomeric transition states. However the models proposed do not represent the real stereochemistry of the transition states, although they do accommodate the experimental results in several cases.[2]

In order to clarify the validity of these models in relation to structural variation in the Grignard reagent, we have investigated the reduction of phenyl alkyl ketones (II) by the following optically active aliphatic Grignard reagents (I) containing an isopropyl or a t-butyl group on the chiral carbon atom: (*S*)-**2,3**-dimethylbutyl- (**2,3**-DMB-), (*S*)-**2,3,3**-trimethylbutyl- (**2,3,3**-TMB-), (*R*)-**3,4**-dimethylpentyl- (**3,4**-DMP-), and (*R*)-**3,4,4**-trimethylpentyl-magnesium chloride (**3,4,4**-TMPMgCl). The experiments were carried out at 35 °C in diethyl ether: an ethereal solution of the carbonyl compound was added to a slight excess (about 10%) of the Grignard reagent (I; $n = 1$) and the mixture was refluxed for 1 h. The reverse addition procedure was adopted for compounds (I; $n = 2$).

The reactions proceeded with high conversions ($\geqslant$90%) yielding both reduction (III) and addition (IV) products, their relative amounts depending essentially on the structures of compounds (I) and (II) (Table 1). In particular (i) for the same ketone, the amount of reduction product (III) decreases with increasing size of R in compound (I; $n = 1$) and seems to be independent of the structure of compound (I; $n = 2$); (ii) for the same Grignard reagent, the reduction yields are dependent on the structure of compound (II); isopropyl phenyl ketone is reduced in the lowest yield.

The carbinols (III) were optically active; the reductions of phenyl t-butyl ketone by (*S*)-**2,3**-DMBMgCl and of isopropyl phenyl ketone by (*R*)-**3,4,4**-TMPMgCl yielded the (*R*)-carbinols, and in all the other cases compound (III) had the absolute *S*-configuration (Table 2).

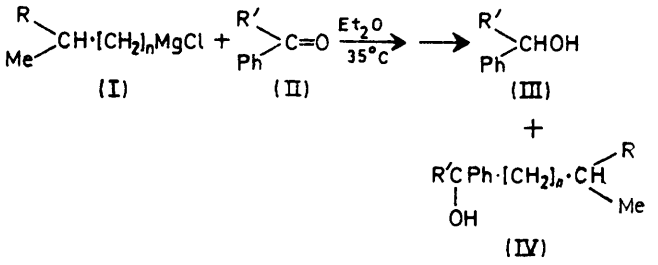
By comparing these results with those previously

[1] Part VII, G. P. Giacomelli, R. Menicagli, and L. Lardicci, *J. Amer. Chem. Soc.*, in the press.

[2] J. D. Morrison and H. S. Mosher, 'Asymmetric Organic Reactions,' Prentice-Hall, Englewood Cliffs, New Jersey, 1971, pp. 177—202 and references therein.

reported,[3,4] we observe that: (i) the stereoselectivity of reduction increases when R in compound (I; $n = 1$) is changed from Et to Pr^i or Bu^t, with the exception that the reduction of t-butyl phenyl ketone by (*S*)-2,3-DMBMgCl occurs with a very low stereoselectivity; (ii) the extent of asymmetric reduction is not directly related to the distance of the chiral centre from the metal atom; in fact the reduction of phenyl t-butyl ketone occurs with higher stereoselectivity with (*R*)-3,4-DMPMgCl than with (*S*)-2,3-DMBMgCl (Table 2). High values of $\Delta\Delta F^*$ (*ca.* 1.0 kcal mol^{-1}) † are involved in the reduction of isopropyl phenyl ketone by (*S*)-2,3-DMBMgCl and (*S*)-2,3,3-TMBMgCl (Table 2).

TABLE 1



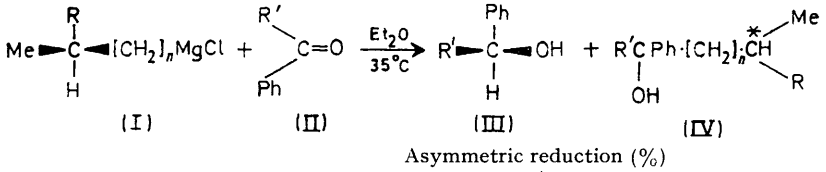
Entry no.	Grignard reagent (I) n	R	Ketone (II) R′	Conversion [a] (%)	Yields [a] (%) (III)	(IV)
1 [b]	1	Et	Et		84	16
2 [b]			Pr^i		87	13
3 [b]			Bu^t		97	3
4		Pr^i	Et	100	60	40
5			Pr^i	100	53	47
6			Bu^t	100	84	16
7		Bu^t	Et	89	45	55
8			Pr^i	97	18	82
9			Bu^t	97	53	47
10 [c,d]	2	Et	Pr^i	82	10	90
11 [c]			Bu^t	100	83	17
12 [c]		Pr^i	Pr^i	98	9	91
13 [c]			Bu^t	95	80	20
14 [c,e]		Bu^t	Pr^i	100	8	92
15 [c]			Bu^t	95	82	18

[a] Determined by g.l.c. analyses on the crude products. [b] See ref. 3. [c] Reverse addition. [d] See ref. 4. [e] See ref. 9.

Although many contributions to the understanding of the mechanism of reaction between Grignard reagents and ketones have been published recently,[5,6] no systematic investigation has been carried out on the factors controlling reduction and addition processes in relation to the nature both of the Grignard reagent and of the carbonyl substrate. On the basis of mechanisms generally accepted,[5,6] there is however no doubt that steric and electronic factors play an important role in determining the course of the reaction. From this point of view, electronic factors, *i.e.* the electron-donating power of the alkyl groups of compound (I), should favour the reduction process: consequently the yields of compound (III) should increase when the alkyl group R in compound (I; $n = 1$) is changed in the order Et < Pr^i < Bu^t. However, the experimental findings (Table 1) are not in agreement with these considerations. The data seem to indicate that the bulk of the groups surrounding the β-hydrogen atom of the Grignard reagent determines the extent of reduction by hindering the transfer of the hydrogen atom in the transition state. When compound (I) is γ-branched, the ratio of reduction to addition seems to depend only on the nature of the ketone (Table 1).

On the basis of the effect of the bulk of the alkyl group R′ in compound (II), the amount of addition product would be expected to decrease in the order R′ = Et < Pr^i < Bu^t. Surprisingly, this order is not always followed (Table 1) and in the reaction of isopropyl phenyl ketone with 2,3,3-TMBMgCl the carbinol (IV) is actually the main product. This observation

TABLE 2



Grignard reagent n	R	R′ = Et %	R′ = Et $\Delta\Delta F^*$/kcal mol^{-1}	R′ = Pr^i %	R′ = Pr^i $\Delta\Delta F^*$/kcal mol^{-1}	R′ = Bu^t %	R′ = Bu^t $\Delta\Delta F^*$/kcal mol^{-1}
		Asymmetric reduction (%)					
1	Et [a]	6	−0.07	24	−0.30	16	−0.20
	Pr^i	14	−0.17	67	−0.99	[2] [b]	+0.02
	Bu^t	25	−0.31	65	−0.95	36	−0.46
2	Et			11 [c]	−0.14	3	−0.04
	Pr^i			16	−0.20	14	−0.17
	Bu^t			[48] [b,d]	+0.64	10	−0.12

[a] See ref. 3. [b] Brackets indicate configuration opposite to that in the equation. [c] See ref. 4. [d] See ref. 9.

† $\Delta\Delta F^*$ is calculated from the equation: $\Delta\Delta F^* = -RT\ln k_S/k_R = -RT\ln [(S)]/[(R)]$, where k_S and k_R are the rate constants for the processes leading to (*S*)- and (*R*)-carbinols, respectively.[1]

[3] R. MacLeod, F. J. Welch. and H. S. Mosher, *J. Amer. Chem. Soc.*, 1960, **82**, 876.

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

[5] B. Denise, J. Ducom, and J. F. Fauvarque, *Bull. Soc. chim. France*, 1972, 990.

[6] E. C. Ashby, J. Laemmle, and H. M. Neumann, *Accounts Chem. Res.*, 1974, **7**, 272.

might be connected with differences in steric and electronic requirements of the phenyl group depending on the structure of R'.[2]

However, the influence of the structure of the carbonyl substrate on the course of the reaction is hard to rationalize with confidence, and the overall results confirm that the reaction follows complex mechanistic pathways. It thus appears hazardous to interpret the stereochemical data in terms of pictures which are not complete, even though they can accommodate some results.

The data reported in Table 2 show that, whatever the structure of R in the optically active Grignard reagent, the extent of asymmetric reduction increases when R' in the ketone is changed from Et to Pr^i and then decreases with the change from Pr^i to Bu^t; these results are analogous to previous observations in the reduction of the same ketones by (+)-tris-[(*S*)-2-methylbutyl]aluminium.[7] The stereoselectivity of some of these processes is the highest encountered with reducing agents having a completely aliphatic structure, even when the asymmetric carbon atom in compound (I) is in the γ-position.[3,4,7-9]

Simple considerations of conformational analysis based on Whitmore's cyclic mechanism [2] do not predict correctly the absolute configuration of the predominant enantiomer in compound (III) in all the cases investigated (Table 2), although the general trend may be rationalized in terms of the effective sizes of the groups being compressed in the transition states.[7,10] The greater the difference in bulk between the alkyl groups on the chiral carbon atom in compound (I), the greater in general is the stereoselectivity of the reduction, even when the asymmetric carbon atom is in the γ-position with respect to the magnesium atom (Table 2). In this last case it is further confirmed that the essential feature of these asymmetric reductions is the difference between the chiral environments of the two diastereotopic β-hydrogen atoms.[9]

At present no rationalization of the stereochemical paths can be offered. Indeed, the situation may be further complicated by solvation effects, which could change in relation to the structure of the Grignard reagent (I) employed. The presence of the solvent in the transition state might thus be responsible for the formation of the ' wrong ' enantiomer in some cases.

EXPERIMENTAL

G.l.c. analyses were performed on a Perkin-Elmer F 30 instrument, with flame ionization detectors (200 × 0.29 cm column packed with 8% Carbowax 20M + 2% KOH on 80—100 mesh Chromosorb W, at 160 °C; 21 ml min^{-1} N_2 flow rate). Preparative g.l.c. was carried out on a Perkin-Elmer F 21 instrument (180 × 0.8 cm column, packed with 20% butanediol succinate on 45—60 mesh Chromosorb W, at 180 °C; 300 ml min^{-1} N_2 flow rate). Optical rotations were measured on a Schmidt–Haensch polarimeter (1 dm tubes). Mass spectra were recorded with a Hitachi-Perkin-Elmer RMU-6L instrument at 70 eV.

The alkyl phenyl ketones were distilled under nitrogen before use, and their purity was checked by g.l.c. All reactions were carried out in an atmosphere of dry, purified nitrogen. The addition products (IV) were characterized by their mass spectra.

(+)-(S)-1-*Chloro*-2,3-*dimethylbutane*.[11]— (+)-(*S*)-2,3-Dimethylbutan-1-ol, n_D^{25} 1.4191, $[\alpha]_D^{25}$ +2.71° (neat), in pyridine solution, was converted in 82% yield into (+)-(*S*)-1-chloro-2,3-dimethylbutane, b.p. 80° at 200 mmHg, n_D^{25} 1.4202, $[\alpha]_D^{25}$ +4.84°, by treatment with thionyl chloride at 80—90 °C for 10 h.

(+)-(S)-1-*Chloro*-2,3,3-*trimethylbutane*.[12]— Analogously (+)-(*S*)-2,3,3-trimethylbutan-1-ol, n_D^{25} 1.4280, $[\alpha]_D^{25}$ +24.59° (*c* 2.32 in EtOH) yielded 70% of (+)-(*S*)-1-chloro-2,3,3-trimethylbutane, b.p. 96° at 160 mmHg, n_D^{25} 1.4288, $[\alpha]_D^{25}$ +30.31° (neat).

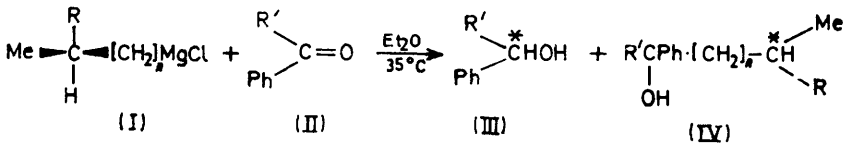
(+)-(R)-1-*Chloro*-3,4-*dimethylpentane*.[11]— (+)-(*S*)-1-Chloro-2,3-dimethylbutane, $[\alpha]_D^{25}$ +4.84°, was converted into the corresponding Grignard reagent, which was then carboxylated to yield 86% of (+)-(*R*)-3,4-dimethylpentanoic acid, $[\alpha]_D^{25}$ +5.94° (neat). Reduction ($LiAlH_4$) afforded (93% yield) (+)-(*R*)-3,4-dimethylpentan-1-ol, n_D^{25} 1.4267, $[\alpha]_D^{25}$ +10.40° (neat), which was diluted with pyridine and treated with thionyl chloride at 90 °C for 10 h to give (69% yield) (+)-(*R*)-1-chloro-3,4-dimethylpentane, b.p. 103° at 190 mmHg, n_D^{25} 1.4278, $[\alpha]_D^{25}$ +16.54° (neat).

(+)-(R)-1-*Chloro*-3,4,4-*trimethylpentane*.[12]—The Grignard reagent from (+)-(*S*)-1-chloro-2,3,3-trimethylbutane, $[\alpha]_D^{25}$ +29.95° (neat), was converted (84% yield) into (+)-(*R*)-3,4,4-trimethylpentanoic acid, $[\alpha]_D^{25}$ +12.15° (*c* 2.67 in EtOH) by treatment with solid CO_2. The acid was reduced (96% yield) with $LiAlH_4$ to (+)-(*R*)-3,4,4-trimethylpentan-1-ol, b.p. 84° at 14 mmHg, n_D^{25} 1.4334, $[\alpha]_D^{25}$ +27.45° (*c* 3.32 in EtOH), which, diluted with pyridine and treated with thionyl chloride, yielded 74% of (+)-(*R*)-1-chloro-3,4,4-trimethylpentane, b.p. 84° at 60 mmHg, n_D^{25} 1.4347, $[\alpha]_D^{25}$ +39.16° (neat).

Asymmetric Reduction of the Alkyl Phenyl Ketones (II).— (a) *With* (S)-2,3-*dimethylbutylmagnesium chloride* (I; $n = 1$; R = Pr^i). The following procedure (entry 5a) is representative of the experiments carried out with (I; $n = 1$) (Table 3). To an ethereal solution of the Grignard reagent from (+)-(*S*)-1-chloro-2,3-dimethylbutane (7.54 g, 62.5 mmol), $[\alpha]_D^{25}$ +4.84° (neat), isopropyl phenyl ketone (8.34 g, 56.2 mmol) in anhydrous ether (50 ml) was added dropwise. The mixture was refluxed for 1 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) and of the addition product, 3,5,6-trimethyl-3-phenylheptan-3-ol, *m/e* 216 (10.6%, $M^+ - H_2O$), 191 (100), 173 (27.0), 149 (69.4), 131 (43.5), 121 (39.4), 71 (85.9), and 43 (85.6). The mixture was separated by preparative g.l.c. to yield (−)-(*S*)-2-methyl-1-phenylpropan-1-ol, b.p. 102° at 18 mmHg, $[\alpha]_D^{25}$ −15.89° (*c* 5.35 in Et_2O).

[7] G. P. Giacomelli, R. Menicagli, and L. Lardicci, *J. Org. Chem.*, 1973, **38**, 2370.
[8] G. P. Giacomelli, L. Lardicci, and R. Santi, *J. Org. Chem.*, 1974, **39**, 2736.
[9] L. Lardicci and G. P. Giacomelli, *J.C.S. Perkin I*, 1974, 337.
[10] J. D. Morrison, ' Survey of Progress in Chemistry,' ed. A. F. Scott, Academic Press, New York, 1966, vol. 3, p. 166.
[11] L. Lardicci, R. Rossi, S. Pucci, M. Aglietto, C. Botteghi, and P. Pino, *Chimica e Industria*, 1968, **50**, 227.
[12] A. M. Caporusso, G. P. Giacomelli, and L. Lardicci, *Atti Soc. Toscana Sci. Nat. (Pisa)*, 1973, **A80**. 40.

TABLE 3



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

Entry no.	Grignard reagent (I) R	n	Optical purity (%)	R′	Config.	Carbinol (III) recovered α_D^{25} (l = 1) (°)	c(Et_2O)	$[\alpha]_D^{25}$	Optical purity[a] (%)	Asymmetric reduction[b] (%)
10[c]	Et	2	95.9[d]	Pr^i	(−)-(*S*)	0.32	6.07	5.27	11.0	11.5
11			95.9[d]	Bu^t	(−)-(*S*)	0.09	10.28	0.87	2.4	2.5
11			95.9[d]		(−)-(*S*)	0.14	14.48	0.97	2.7	2.8
4	Pr^i	1	48.7	Et	(−)-(*S*)	1.92	Neat	1.94	6.8	14.0
5			48.7	Pr^i	(−)-(*S*)	0.85	5.35	15.89	33.3	68.4
5			62.4		(−)-(*S*)	3.05	15.78	19.33	40.5	64.9
6			48.7	Bu^t	(+)-(*R*)	0.09	21.63	0.42	1.2	2.5
6			48.7		(+)-(*R*)	0.02	7.75	0.26	0.7	1.4
12		2	48.7	Pr^i	(−)-(*S*)	0.17	4.44	3.83	8.0	16.4
13			48.7	Bu^t	(−)-(*S*)	0.33	14.32	2.30	6.3	12.9
13			48.7		(−)-(*S*)	0.16	6.09	2.63	7.3	15.0
7	Bu^t	1	53.4	Et	(−)-(*S*)	3.81	Neat	3.84	13.4	25.1
8			84.0	Pr^i	(−)-(*S*)	1.45	5.46	26.56	55.7	66.3
8			59.4		(−)-(*S*)	1.34	7.37	18.18	38.1	64.1
9			84.0	Bu^t	(−)-(*S*)	0.77	7.07	10.89	30.1	35.8
9			59.4		(−)-(*S*)	0.72	9.02	7.98	22.0	37.0
14[e]		2	84.0	Pr^i	(+)-(*R*)	1.04	5.42	19.19	40.2	47.8
15			58.7	Bu^t	(−)-(*S*)	0.19	9.57	1.98	5.5	9.4
15			58.7		(−)-(*S*)	0.21	9.54	2.20	6.1	10.4

[a] See ref. 8. [b] Corrected for the minimum optical purity of the Grignard reagent. [c] See ref. 4. [d] L. Lardicci and L. Conti, *Gazzetta*, 1962, **92**, 428. [e] See ref. 9.

(b) *With* (R)-3,4-*dimethylpentylmagnesium chloride* (I; $n = 2$; R = Pr^i). This procedure (entry 12) is typical of the runs carried out with (I; $n = 2$) (Table 3). To an ethereal solution (20 ml) of isopropyl phenyl ketone (4.95 g, 33.4 mmol) the Grignard reagent prepared from (+)-(*R*)-1-chloro-3,4-dimethylpentane (5.00 g, 37.1 mmol), $[\alpha]_D^{25}$ +16.54° (neat), was added dropwise. After refluxing for 1 h, the mixture was hydrolysed and extracted with ether. G.l.c. analysis of the crude product showed the presence of the carbinol (III) and the addition product (IV), 3,6,7-trimethyl-3-phenyloctan-3-ol, *m/e* 230 (4.1%, $M^+ - H_2O$), 205 (91.8), 187 (6.8), 149 (78.1), 117 (100), 105 (41.1), 91 (37.0), 83 (82.2), and 43 (63.0). After preparative g.l.c., (−)-(*S*)-2-methyl-1-phenylpropan-1-ol, $[\alpha]_D^{25}$ −3.83° (*c* 4.44 in Et_2O), was recovered.

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