Alkyl Metal Asymmetric Reduction. III.[1,2] The Stereochemistry of Alkyl Phenyl Ketone Reductions by Chiral Organoaluminum Compounds

GIAMPAOLO GIACOMELLI, RITA MENICAGLI, AND LUCIANO LARDICCI*

Istituto di Chimica Organica, Facoltà di Scienze M. F. N., Università di Pisa, 56100 Pisa, Italy

Received January 19, 1973

The asymmetric reduction of a series of alkyl phenyl ketones by optically active organoaluminum compounds, having β-branched alkyl groups, has been studied. The reactions, which have been carried out at 0°, afforded (*S*)-alkylphenylcarbinols in good yield. The extent of the asymmetric reduction was found to depend on the structure of the ketone employed and to be affected by the presence of a donor ligand to the aluminum atom. Moreover the reduction of isopropyl phenyl ketone by chiral solvates of triisobutylaluminum occurs with low but definite asymmetric induction. The overall results, which are consistent with a β-hydride transfer from the alkyl group of the organoaluminum compound to the carbonyl carbon atom, are interpreted as indicating that, in the presence of ethers, the reaction occurs without prior dissociation of the ligand from the aluminum atom in cyclic six-membered-ring transition states. The stereoselectivity of the reduction process is rationalized in terms of steric and electronic interactions in competing transition states for the hydrogen-transfer step.

The steric course of asymmetric Grignard reductions has been extensively investigated during the last 20 years[3,4] to establish direct relationships among the extent of asymmetric induction and the nature of carbonyl substrates and chiral reducing agents. High stereoselectivity has been observed with chiral Grignard reagents having phenyl groups,[3f,5] while (+)-(*S*)-2-methylbutylmagnesium halides yield carbinols with lower extents of asymmetric reduction.[3d]

Although the ability of organoaluminum reagents to reduce carbonyl compounds has been well established,[6] this reaction has thus far attracted attention more for mechanistic aspects than for stereochemical implications.[7] Only recently has the occurrence of asymmetric induction phenomena in the reduction of prochiral ketones by optically active organoaluminum compounds been reported.[1,2,8]

In continuing our investigation[1,2] on this reaction we report now more accurate details on the stereochemistry of the reduction of alkyl phenyl ketones by (*S*)-2-methylbutylaluminum derivatives and triisobutylaluminum chiral solvates and, in this connection, on the role of the solvent.

Experimental Section

Materials.—*tert*-Butyl phenyl ketone was prepared (60% yield) by chromic oxidation[9] of *tert*-butylphenylcarbinol prepared in a 60% yield by the method of Winstein and Morse.[10] The other ketones were commercial products and were purified through the semicarbazone derivatives.[11] Triisobutylaluminum was obtained from Texas Alkyls, Inc., and was purified by distillation under vacuum. (+)-Tris[(*S*)-2-methylbutyl]aluminum and (+)-tris[(*S*)-2-methylbutyl]aluminum diethyl etherate of high optical purity were prepared as previously described.[12,13] (+)-Tris[(*S*)-2-methylbutyl]aluminum of low optical purity was obtained diluting the above mentioned samples with racemic product. All the organoaluminum compounds were distilled under nitrogen and stored in sealed glass vials, in weighed amounts.

Tetrahydrofuran was purified according to the procedure of Böhme and Schürhoff,[14] distilled, and stored over sodium wire. Glpc analyses were performed on a C. Erba Fractovap Model GT instrument with flame ionization detectors, using 200 × 0.30 cm columns packed with 10% butanediol succinate (BDS) on 60–80 mesh Chromosorb W, at 150°. All rotations, unless otherwise indicated, were taken on a Schmidt-Haensch polarimeter with sensitivity of ±0.005° in 0.5- and 1-dm tubes.

Asymmetric Reductions of Alkyl Phenyl Ketones. A. By (+)-Tris[(*S*)-2-methylbutyl]aluminum in Pentane. 1.—In a typical run, a solution of 0.780 g (5.26 mmol) of isopropyl phenyl ketone in 7 ml of anhydrous pentane was added rapidly, under nitrogen, to a solution of 1.414 g (5.88 mmol) of (+)-tris[(*S*)-2-methylbutyl]aluminum, $[\alpha]^{25}D$ +24.82° (neat),[12] in 13 ml of pentane, cooled at 0°, in a flame-dried two-neck 100-ml flask fitted with a reflux condenser, a dropping funnel, and a magnetic stirrer. An immediate yellow-orange coloration developed and faded quickly. After 2 hr, the resulting mixture was cautiously hydrolyzed with dilute sulfuric acid (pH 5) and the organic products were extracted with purified ether. The crude product was shown by glpc analysis to contain 3.6% of ketone. Distillation afforded 0.670 g (85%) of isopropylphenylcarbinol (96.5% pure by glpc analysis), bp 104° (18 mm), $n^{25}D$ 1.5114, $[\alpha]^{25}D$ −15.02° (*c* 4.68, ether).[3f]

2.—(+)-Tris[(*S*)-2-methylbutyl]aluminum, $[\alpha]^{25}D$ +14.06° (neat), was treated at 0° with *tert*-butyl phenyl ketone in pentane to yield 99% of *tert*-butylphenylcarbinol (99.8% pure by glpc analysis), bp 111° (18 mm), mp 55°, $[\alpha]^{25}D$ −4.53° (*c* 4.86, ether).[3f]

Analogously, (+)-tris[(*S*)-2-methylbutyl]aluminum, $[\alpha]^{25}D$ +6.89° (neat), afforded 88% of *tert*-butylphenylcarbinol (pure by glpc analysis), $[\alpha]^{25}D$ −2.21 (*c* 15.39, ether).

3.—At 0°, to 1.643 g (6.83 mmol) of (+)-tris[(*S*)-2-methylbutyl]aluminum, $[\alpha]^{25}D$ +26.34° (neat), in 10 ml of pentane was added rapidly 1.038 g (6.40 mmol) of *tert*-butyl phenyl ketone in 10 ml of pentane. After 1 min, the reaction mixture was hydrolyzed and the organic product was recovered and distilled to give 0.879 g (84%) of the carbinol (99.6% pure), $[\alpha]^{25}D$ −8.46° (*c* 7.68, ether).

(1) Part I: G. P. Giacomelli, R. Menicagli, and L. Lardicci, *Tetrahedron Lett.*, 4135 (1971).

(2) Part II: L. Lardicci, G. P. Giacomelli, and R. Menicagli, *Tetrahedron Lett.*, 687 (1972).

(3) (a) H. S. Mosher and E. La Combe, *J. Amer. Chem. Soc.*, **72**, 3994, 4991 (1950); (b) H. S. Mosher, J. E. Stevenot, and D. O. Kimble, *ibid.*, **78**, 4374 (1956); (c) W. M. Foley, F. J. Welch, E. M. La Combe, and H. S. Mosher, *ibid.*, **81**, 2779 (1959); (d) R. MacLeod, F. J. Welch, and H. S. Mosher, *ibid.*, **82**, 876 (1960); (e) E. P. Burrows, F. J. Welch, and H. S. Mosher, *ibid.*, **82**, 880 (1960); (f) J. S. Birtwistle, K. Lee, J. D. Morrison, W. A. Sanderson, and H. S. Mosher, *J. Org. Chem.*, **29**, 37 (1964); (g) M. S. Biernbaum and H. S. Mosher, *ibid.*, **36**, 3168 (1971).

(4) (a) J. D. Morrison, D. L. Black, and R. W. Ridgway, *Tetrahedron Lett.*, 985 (1968); (b) J. D. Morrison, A. Tomash, and R. W. Ridgway, *ibid.*, 565 (1969); (c) J. D. Morrison and R. W. Ridgway, *ibid.*, 569 (1969); (d) J. D. Morrison and R. W. Ridgway, *J. Amer. Chem. Soc.*, **91**, 4601 (1969).

(5) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971, pp 187–194.

(6) (a) T. Mole and J. R. Surtees, *Aust. J. Chem.*, **17**, 961 (1964); (b) S. Pasynkiewicz and E. Śliwa, *J. Organometal. Chem.*, **3**, 121 (1965); (c) Y. Baba, *Bull. Chem. Soc. Jap.*, **41**, 2173 (1968); (d) E. C. Ashby and S. H. Yu, *J. Org. Chem.*, **35**, 1034 (1970).

(7) H. Haubenstock and E. B. Davidson, *J. Org. Chem.*, **28**, 2772 (1963).

(8) R. A. Kretchmer, *J. Org. Chem.*, **37**, 801 (1972).

(9) G. P. Giacomelli and L. Lardicci, *Atti Soc. Tosc. Sci. Nat., Pisa, Mem., Ser. A*, **78**, 159 (1971).

(10) S. Winstein and B. K. Morse, *J. Amer. Chem. Soc.*, **74**, 1138 (1952).

(11) C. Djerassi and L. E. Geller, *J. Amer. Chem. Soc.*, **81**, 2789 (1959).

(12) (a) L. Conti, L. Lardicci, and P. Pino, *Chim. Ind. (Milan)*, **43**, 414 (1961); (b) L. Lardicci, G. P. Giacomelli, and L. De Bernardi, *J. Organometal. Chem.*, **39**, 245 (1972).

(13) P. Pino, L. Lardicci, and G. P. Lorenzi, *Ann. Chim. (Rome)*, **48**, 1426 (1958).

(14) H. Böhme and W. Schürhoff, *Chem. Ber.*, **84**, 41 (1951).

B. By (+)-Tris[(*S*)-2-methylbutyl]aluminum Diethyl Etherate.—To 2.446 g (7.77 mmol) of (+)-tris[(*S*)-2-methylbutyl]-aluminum diethyl etherate, $[\alpha]^{28}D$ +22.20°,[13] $[\alpha]^{25}D$ +21.78° (*c* 4.68, pentane), in 15 ml of anhydrous pentane, was added at 0° 1.037 g (7.00 mmol) of isopropyl phenyl ketone in 10 ml of pentane. After 2 hr, the reaction mixture was worked up as above described. The crude carbinol, which was shown to contain 2.3% of ketone (by glpc analysis), yielded for distillation 0.955 g (91%) of isopropylphenylcarbinol (97.7% pure), $n^{25}D$ 1.5114, $[\alpha]^{25}D$ −15.76° (*c* 4.82, ether).

C. By Tris[(*S*)-2-methylbutyl]aluminum Tetrahydrofuranate.—To 1.748 g (7.27 mmol) of (+)-tris[(*S*)-2-methylbutyl]aluminum, $[\alpha]^{25}D$ +24.82° (neat), in 10 ml of pentane was added 0.525 g (7.28 mmol) of tetrahydrofuran in 2 ml of pentane at 0°, and successively 0.970 g (6.55 mmol) of isopropyl phenyl ketone in 8 ml of pentane. Immediately the reaction mixture assumed an intense orange color, which faded slowly. After 2 hr the solution was decomposed with dilute sulfuric acid and extracted with ether. Distillation of the crude product, which contained ketone and carbinol in the ratio 1:6 (by glpc analysis), afforded 0.684 g of isopropylphenylcarbinol (86.0% pure), $n^{25}D$ 1.5119, $[\alpha]^{25}D$ −12.94° (*c* 5.64, ether).

Reduction of α-Tetralone by (+)-Tris[(*S*)-2-methylbutyl]-aluminum.—To 2.580 g (10.73 mmol) of (+)-tris[(*S*)-2-methylbutyl]aluminum, $[\alpha]^{25}D$ +28.73° (neat), in 20 ml of pentane was added at 0° 1.412 g (9.66 mmol) of α-tetralone in 10 ml of pentane. After 2 hr the reaction mixture was hydrolyzed and the organic product was extracted with ether. The crude carbinol, after redistillation, yielded 0.878 g (61%) of α-tetralol (94% pure by glpc analysis on BDS columns at 170°), bp 87° (0.07 mm), $\alpha^{25}D$ (*l* 1) 0.00° (*c* 5.36, benzene).

Asymmetric Reduction of Isopropyl Phenyl Ketone by Chiral Solvates of Triisobutylaluminum. A. With (−)-Sparteine.—To a solution of 1.880 g (9.48 mmol) of triisobutylaluminum in 5 ml of dry pentane was added slowly at 0° 2.210 g (9.44 mmol) of (−)-sparteine, $[\alpha]^{25}D$ −16.27° (*c* 7.03, ethanol),[15] in 5 ml of pentane. The resultant mixture was then treated, at the same temperature, with 1.400 g (9.46 mmol) of isopropyl phenyl ketone in 10 ml of pentane. After 2 hr the reaction mixture was quenched with dilute hydrochloric acid (pH 3) and the organic layer was extracted with ether. After removal of the solvent, the crude carbinol (containing 5.3% of ketone, as shown by glpc analysis) was distilled and 1.170 g (82%) of isopropylphenylcarbinol (94.7% pure), $n^{25}D$ 1.5122, $[\alpha]^{25}D$ −3.55° (*c* 11.27, ether), was recovered.

B. With (+)-(*S*)-(1-Methylpropyl) Ethyl Ether.—To 0.497 g (4.86 mmol) of (+)-(*S*)-(1-methylpropyl) ethyl ether, $[\alpha]^{25}D$ +26.96° (*c* 4.02, isooctane), optical purity (o.p.) 78.7%,[16] was added at 0° a solution of 0.964 g (4.86 mmol) of triisobutylaluminum in 15 ml of pentane, followed by 0.713 g (4.82 mmol) of isopropyl phenyl ketone in 5 ml of pentane. The reaction mixture was hydrolyzed after 2 hr and worked up in the usual manner to give a crude product (95% conversion by glpc analysis) which, after redistillation, afforded 0.524 g (72%) of isopropylphenylcarbinol (95.1% pure), $n^{25}D$ 1.5118, $[\alpha]^{25}D$ −2.10° (*c* 10.48, ether).

C. With (+)-(3*S*,1′*S*)-3-(1′-Methylpropyl)tetrahydrofuran.—To 0.563 g (2.84 mmol) of triisobutylaluminum in 10 ml of anhydrous pentane was added at 0° a solution of 0.358 g (2.80 mmol) of (+)-(3*S*,1′*S*)-3-(1′-methylpropyl)tetrahydrofuran, $[\alpha]^{25}D$ +17.17° (*c* 1.18, *n*-heptane) [(*S*,*S*) ≥ 90%],[17] in 5 ml of pentane and then 0.400 g (2.70 mmol) of isopropyl phenyl ketone in 5 ml of pentane. The mixture, after hydrolysis (2 hr), was extracted continuously with ether to give a crude carbinol (92% conversion by glpc analysis), which, after accurate purification, yielded 0.234 g (58%) of isopropylphenylcarbinol, $[\alpha]^{25}_{589}$ −0.70° (*c*, 4.67, ether).

Results

The asymmetric reductions have been carried out at 0° for 2 hr, in pentane or ethereal solvent, using a slight excess (about 10%), with respect to the alkyl phenyl ketones, of tris[(*S*)-2-methylbutyl]aluminum[12] (Al2MB), tris[(*S*)-2-methylbutyl]aluminum diethyl etherate[13] (Al2MB·OEt_2), tris[(*S*)-2-methylbutyl]aluminum tetrahydrofuranate (Al2MB·THF), or chiral solvates of triisobutylaluminum (Al2MP·L*). The obtained results are summarized in Tables I and II.

It has been previously reported that organoaluminum compounds react with ketones to give addition, reduction, and enolization products.[6] The relative amounts of the addition and reduction products are dependent on the reaction temperature and on the reactants molar ratio, while the enolization reaction seems to be not affected.[6b,c] In the experimental conditions we have adopted, neither addition nor significant enolization reactions occur, the conversion (by glpc) in carbinols being generally ≥90% (Table I).

The reactions are very fast[18] in the absence of donor ligands (*e.g.*, the reduction of *tert*-butyl phenyl ketone is practically complete within 1 min), and also when Al2MB·OEt_2 in pentane is used, although an appreciable retardation is observed in ethereal solvent; however, the reaction rate drops substantially when THF is used.[19]

By inspection of Tables I and II, the following considerations can be made.

(1) All the carbinols have the absolute *S* configuration. The extent of asymmetric reduction is dependent on the structure of the alkyl group in the phenyl ketone employed, increasing in the order of $CF_3 \cong Me < Et < t\text{-}Bu < i\text{-}Pr$.

(2) The stereoselectivity of the reduction is affected by the presence of a donor ligand, a large excess of which does not further change the extent of asymmetric induction.

(3) The decrease in the stereoselectivity of the reduction from isopropyl phenyl ketone to *tert*-butyl phenyl ketone is enhanced in the absence of donor ligands.

(4) The reduction of isopropyl phenyl ketone by Al2MP·L* in pentane solution occurs with low but definite asymmetric induction.

Discussion

Role of the Solvent.—It is generally accepted that, in the absence of donor ligands, the mechanism of the reduction of ketones by organoaluminum compounds with β-branched alkyls is based on the complexation of trialkylaluminum with the ketone (eq 1) followed by an intramolecular hydride transfer from the β carbon of the alkyl group bound to the aluminum to the carbonyl carbon (eq 2).[6b-d,7] Such a mechanism, adopted for the reduction of benzophenone by triisobutylaluminum in diethyl ether solvent,[6d] was recently tested by asymmetric induction studies carried out with optically active beryllium and aluminum compounds.[1]

(15) H. Nozaki, T. Aratani, T. Toraya, and R. Noyori, *Tetrahedron*, **27**, 905 (1971).

(16) E. Chiellini, private communication.

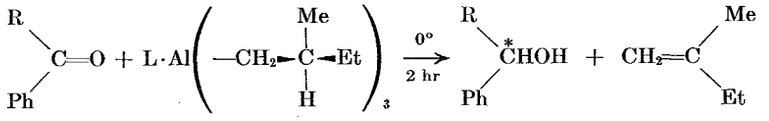
(17) C. Botteghi, G. Ceccarelli, and G. Consiglio, *J. Prakt. Chem.*, **314**, 840 (1972).

(18) According to previous observations of many workers,[6] when the ketone is added to the organoaluminum solution, a transient red-yellow color, which generally fades within a few minutes, is observed. Such a phenomenon should be related to an "ate-complex" [G. Wittig, *Quart. Rev., Chem. Soc.*, **20**, 191 (1966)], intermediate in product formation, although any consideration appears to be hazardous owing to other possible competing side equilibria.

(19) After 2 hr at 0° Al2MP·THF reduces isopropyl phenyl ketone in 89% conversion in pentane solution, and in conversion in 10% tetrahydrofuran as solvent.

TABLE I

ASYMMETRIC REDUCTION OF PHENYL ALKYL KETONES BY OPTICALLY ACTIVE ORGANOALUMINUM COMPOUNDS

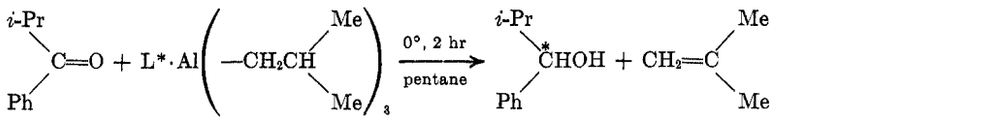


Run	R	Registry no.	L	Registry no.	Solvent	Conversion [a] %	Chemical purity [b] %	S Carbinol: Registry no.	S Carbinol: Optical rotation, $\alpha^{25}D$, deg, ether (l, c)	S Carbinol: $[\alpha]^{25}D$	S Carbinol: $[\alpha]^{25}D$ [c]	Optical purity, [d] %	Asymmetric reduction, [e] %
1[f]	Me	98-86-2		4023-25-0	Pentane	94	87.0	1445-91-6	−0.96 (0.5, neat)	−1.90	−2.18	5.0	5.9
2[g]			Et_2O	18902-57-3	Ether	95	99.4		−1.28 (0.5, neat)	−2.53	−2.55	5.8	5.9
3[h]	Et	93-55-0			Pentane	98	99.4	613-87-6	−2.54 (1, neat)	−2.56	−2.58	8.9	13.2
4[f]					Pentane	96	97.8		−1.56 (0.5, neat)	−3.15	−3.22	11.2	13.2
5[i]			Et_2O		Pentane	98	98.8		−1.42 (0.5, neat)	−2.86	−2.89	10.0	10.5
6[i]			Et_2O		Pentane	98	99.2		−1.32 (0.5, neat)	−2.66	−2.68	9.3	9.5
7[i]			Et_2O		Ether	97	96.8		−2.31 (1, neat)	−2.33	−2.41	8.4	8.7
8[i]			Et_2O		Ether	95	94.8		−1.06 (0.5, neat)	−2.14	−2.26	7.9	8.2
9[j]			THF	39814-22-7	Pentane	67	61.9		−0.25 (1, 9.15)	−2.73	−4.41	8.6[k]	11.7
10[h]	*i*-Pr	611-70-1			Pentane	96	98.4	34857-28-8	−0.71 (1, 5.04)	−14.07	−14.30	30.0	44.4
11[j]					Pentane	96	96.5		−0.73 (1, 4.86)	−15.02	−15.56	32.6	44.3
12[i]			Et_2O		Pentane	98	97.7		−0.76 (1, 4.82)	−15.76	−16.13	33.8	35.2
13[i]			Et_2O		Ether	98	97.7		−0.93 (1, 5.86)	−15.87	−16.24	34.0	35.4
14[j]			THF		Pentane	86	86.0		−0.73 (1, 5.64)	−12.94	−15.04	31.5[l]	42.8
15[h]	*t*-Bu	938-16-9			Pentane	99	99.3	15914-85-9	−0.70 (1, 9.66)	−7.24	−7.29	20.1	29.8
16[f]					Pentane	97	97.0		−0.45 (1, 5.02)	−8.96	−9.24	25.5	29.9
17[i]			Et_2O		Pentane	∼100	∼100		−0.86 (1, 7.54)	−11.40	−11.40	31.5	32.8
18[i]			Et_2O		Ether	97	97.1		−1.03 (1, 9.37)	−10.99	−11.31	31.2	32.6
19[j]			THF		Pentane	96	96.1		−0.90 (1, 9.13)	−9.85	−10.25	28.3	38.4
20[j]			THF		Pentane	89	∼100		−0.46 (1, 4.49)	−10.24	−10.24	28.3	38.4
21[f]	CF_3	434-45-7			Pentane	∼100	∼100	340-06-7	+0.103 (1, 5.94, benzene)[m]	+1.73	+1.73	5.1[n]	6.0
22[f]					Pentane	∼100	∼100		+0.081 (1, 4.56, benzene)[m]	+1.77	+1.77	5.2[n]	6.1
23[i]			Et_2O		Pentane	∼100	∼100		+0.96 (0.5, neat)			4.7[o]	4.9

[a] Based on glpc analyses of the crude products. [b] Estimated from the gas chromatograms of the products after redistillation, other impurities being the ketone. [c] Corrected for the per cent purity of the carbinol. [d] See ref 3f. [e] Corrected for the minimum optical purity of the organoaluminum compound used. [f] (+)-Tris[(*S*)-2-methylbutyl]aluminum, o.p. 85.2%. [g] (+)-Tris[(*S*)-2-methylbutyl]aluminum diethyl etherate, o.p. 98.0%. [h] (+)-Tris[(*S*)-2-methylbutyl]aluminum, o.p. 67.5%. [i] (+)-Tris[(*S*)-2-methylbutyl]aluminum diethyl etherate, o.p. 96.9%. [j] (+)-Tris[(*S*)-2-methylbutyl]aluminum, o.p. 73.6%. [k] Assuming $[\alpha]^{25}D$ +51.1° (*c* 7.55, ether) for the enantiomerically pure carbinol in the presence of *ca.* 30% of the ketone. [l] This value, corrected on the basis of the rotatory power of an ethereal solution containing 86% of the carbinol (o.p. 28%) and 14% of the ketone, is 30.6. [m] Measured with a spectrophotometric polarimeter, Perkin-Elmer Model 141, at 365 nm. [n] Assuming $[\alpha]^{25}_{365}$ +34.0° (*c* 6.41, benzene) for the enantiomerically pure carbinol. [o] D. M. Feigl and H. S. Mosher, *J. Org. Chem.*, **33**, 4242 (1968).

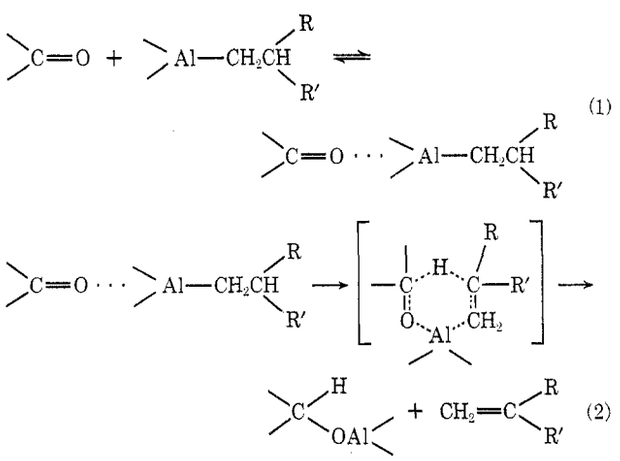
TABLE II

ASYMMETRIC REDUCTION OF ISOPROPYL PHENYL KETONE BY CHIRAL SOLVATES OF TRIISOBUTYLALUMINUM



Registry no.	L* [α]25D, deg (c, solvent)	Conversion,[a] %	S carbinol: Chemical purity,[b] %	Optical rotation: α25D, deg, ether (l, c)		[α]25D	[α]25D[c]	Optical purity,[d] %
37349-76-1	(−)-Sparteine −16.30 (7.03, ethanol)	95	94.7	−0.80	(2, 11.27)	−3.55	−3.75	7.9
39814-23-8	(+)-(*S*)-*sec*-BuOEt +26.96 (4.02, isooctane)	95	95.1	−0.22	(1, 10.47)	−2.10	−2.21	4.6
39814-24-9	(+)-(3*S*,1′*S*)-3-*sec*-BuTHF +17.17 (1.18 *n*-heptane)	92	93.2	−0.033	(1, 4.67)[e]	−0.70	−0.75	1.6

[a] Based on glpc analyses of the crude products. [b] Evaluated from the gas chromatograms of the products after redistillation (other impurities are the ketone). [c] Corrected for the per cent purity of the carbinol. [d] See ref 3f. [e] Measured with a spectrophotometric polarimeter, Perkin-Elmer Model 141, at 589 nm.



Actually, in the presence of donor ligands, several alternative reaction pathways might be postulated for the reduction of ketones (Scheme I).[6d,20] While no doubt exists about the occurrence of a complex between the organoaluminum compound and the ketone,[6,20] the question arises whether the ligand is displaced from the aluminum alkyl prior to the formation of the complex or partakes in the transition state of the reaction in a pentacoordinate intermediate.

Although the dissociation of organoaluminum etherates (eq 3) does not seem probable, on the basis also of literature data,[21] both paths 3 and 4 could explain the decrease of the reduction rate when the etherates are used, especially in the presence of an excess of donor solvent. The reaction rate should be therefore in relation to the basic strength of the ligand; so the different stereoselectivity in the reduction of ketones by tris[(*S*)-2-methylbutyl]aluminum (Al2MB) and tris-[(*S*)-2-methylbutyl]aluminum etherates (Al2MB·OEt_2, Al2MB·THF) might be explained on the basis of a rate retardation. However, in a clear disagreement, while the reduction rate seems to be effectively related to the ligand basicity, *i.e.* Al2MB > Al2MB·OEt_2 > Al2MB·THF, the asymmetric induction extent does not always follow the same order (Table III).

On the other hand, using diethyl ether as solvent, the reduction rate of the ketones by tris[(*S*)-2-methylbutyl]aluminum diethyl etherate decreases appreciably but the percentage of asymmetric induction does not change (Table I). Moreover these mechanisms (eq 3, 4) are not consistent with the low but definite stereoselectivity observed in the reduction of isopropyl phenyl ketone by chiral solvates of triisobutylaluminum (Table II).

Such results are in better agreement with path 5 (Scheme I), which involves the formation of a penta-

SCHEME I

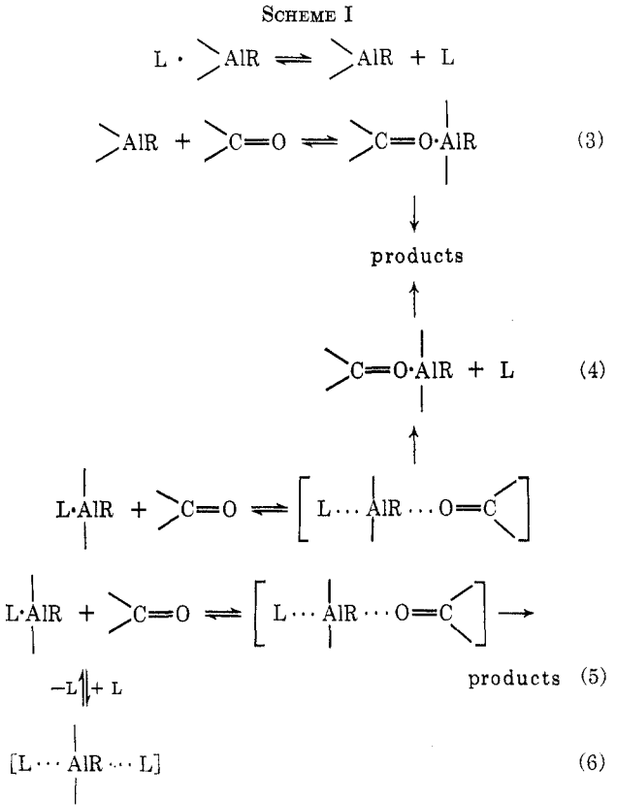


TABLE III

PER CENT ASYMMETRIC REDUCTION[a] OF ALKYL PHENYL KETONES BY OPTICALLY ACTIVE ORGANOALUMINUM COMPOUNDS

Ligand	Me	Et	*i*-Pr	*t*-Bu	CF_3
	6	13	44	30	6
Et_2O	6	9	35	33	5
THF		12	43	38	

[a] Average values.

(20) E. C. Ashby, S. H. Yu, and P. V. Roling, *J. Org. Chem.*, **37**, 1918 (1972).

(21) H. Lehmkuhl and K. Ziegler in "Methoden der Organischen Chemie," Houben-Weil, Ed., Vol. 13, Part 4, Georg Thieme Verlag, Stuttgart, 1970, pp 95–110.

coordinate aluminum in the transition state[6d,20,22] without loss of the initial solvating ligand, which in effect should not be split off but should still remain in the coordination sphere of the aluminum atom. Moreover, since ketone has a weaker basic strength than ether,[23] it seems more reasonable that a transition state having weak ether–aluminum–ketone bonds should proceed to trialkylaluminum etherate rather than to a complex between carbonyl and organoaluminum compounds.[24]

The different rates of the reduction of ketones by the various organoaluminum compounds used can be therefore rationalized on the basis of a different electronegativity of the aluminum atom in the aluminum alkyl and in the etherates.[25] The further decrease of the reduction rate in ethereal solvent might be explained in this case with a competition of ether and ketone in the solvating reaction of the organoaluminum etherate (eq 5, 6).[26]

In view of the above hypothesis the electronegativity of the aluminum atom should control its distance from the carbonyl oxygen in the transition state, since the stronger the coordination of the ligand the longer this distance. Therefore the steric interactions in the six-membered transition states (eq 2) and consequently the stereoselectivity of the reduction should change in relation to the Lewis base strength and to the steric bulk properties of the ligand (Table I).

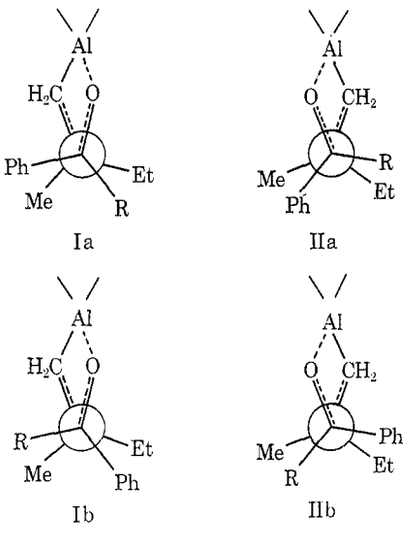
In any case, all the mechanisms (Scheme I) should involve a cyclic intramolecular hydride transfer (eq 2) rather than a reduction by dialkylaluminum hydride,[6d,7] formed either from trialkylaluminum or as a consequence of the ketone attack, since the monohydride species are in very low concentration at 0° in hydrocarbon solvents,[27,28] and quite absent in the presence of donor ligands; in fact, organoaluminum etherates do not form the corresponding hydride even at 90°.[29]

Conformational Analysis.—Table III reports the extent of asymmetric reduction of the alkyl phenyl ketones by optically active organoaluminum compounds. It is to be noted that the general trend in the extent of asymmetric reduction resembles that encountered in the reduction of the same series of ketones by (*S*)-2-methylbutylmagnesium halides.[3a-e]

Simple considerations of conformational analysis,[3,5] based on Whitmore's cyclic mechanism, permit the correct prediction of the absolute configuration of the predominant enantiomer, but they are not able to explain the trend in the series. In fact, if the extent of asymmetric reduction should depend on the difference in steric bulk between the phenyl and the alkyl group of ketones, the stereoselectivity of the reduction should decrease as the bulk of the alkyl group increases.[5] On the other hand, a conformational approach based on recent suggestions which take into account electronic interactions too[30] does not clarify the drop in the stereoselectivity when the alkyl is a *tert*-butyl group, even if it might explain the higher asymmetric induction in the phenyl alkyl series as the alkyl group changes from methyl to isopropyl.

On the basis of our previous considerations on the mechanism of the reduction, which involves a cyclic intramolecular hydride transfer (eq 2), and considering that the coordinate bond between aluminum and oxygen atom is to be relatively loose to minimize the rigidity consequent to a cyclic model,[30] only four reacting conformations, viewed along the C···H–C* axis, are to be considered (Scheme II).

SCHEME II



The transition states Ia and IIa lead to *S* carbinol; the first is reasonably the stablest both for steric and electronic requirements. In fact, in Ia the aluminum atom (CH_2–$Al^{\delta+}$) is placed between two negative dipoles (C–$O^{\delta-}$, C–$Ph^{\delta-}$)[30] and the phenyl group is in a quasi-anti position with respect to the ethyl group of the aluminum compound. On the contrary, Ib and IIb lead to *R* alcohol; for electronic reasons,[30] the conformation IIb has the lowest energy, although the steric interactions are similar in these two cases. Since the conformation Ia is more favored than IIb for steric requirements,[31] the carbinol from asymmetric induction must have the *S* configuration. This picture, however, does not satisfactorily predict the observed trend of asymmetric reduction. In this respect a helpful suggestion is to consider that, as the alkyl group increases in bulk, the conformational mobility of the phenyl group decreases, its size increasing formally. As confirmed by inspection of molecular models, the steric hindrance of the alkyl group prevents the free rotation of the phenyl group more in the conformation IIb than

(22) Although organoaluminum compounds appear generally to be tetracoordinate in donor solvents, the existence of pentacoordinate intermediates has been postulated, as transition states, in alkyl group exchange reactions[24] and observed as dimethyl sulfoxide adducts [C. A. Smith and M. G. H. Wallbridge, *J. Chem. Soc. A*, 2675 (1970)]. On the other hand, pentacoordinate organomagnesium compounds have been invoked to explain the influence on the addition rate of dimethylmagnesium to benzophenone [H. O. House and J. E. Oliver, *J. Org. Chem.*, **33**, 929 (1968)].

(23) T. Kagiya, Y. Sumida, and T. Inoue, *Bull. Chem. Soc. Jap.*, **41**, 767 (1968).

(24) (a) T. Mole, *Aust. J. Chem.*, **16**, 801 (1963); (b) T. Mole, *ibid.*, **18**, 1183 (1965); (c) N. S. Ham, E. A. Jeffery, T. Mole, and J. K. Saunders, *ibid.*, **20**, 2641 (1967).

(25) A. C. M. Wanders and E. Konijnenberg, *Tetrahedron Lett.*, 2081 (1967).

(26) It is noteworthy that a decrease in rate was observed in the alkyl group exchange reactions among different metal alkyls,[24c] as the ratio ether: organoaluminum compound is increased from 1:1.

(27) G. Pajaro and L. Baldi, *Gazz. Chim. Ital.*, **91**, 493 (1961).

(28) K. W. Egger, *J. Amer. Chem. Soc.*, **91**, 2867 (1969).

(29) L. Lardicci, L. Lucarini, P. Palagi, and P. Pino, *J. Organometal. Chem.*, **4**, 341 (1965).

(30) D. Nasipuri, C. K. Ghosh, P. R. Mukherjee, and S. Venkataraman, *Tetrahedron Lett.*, 1587 (1971).

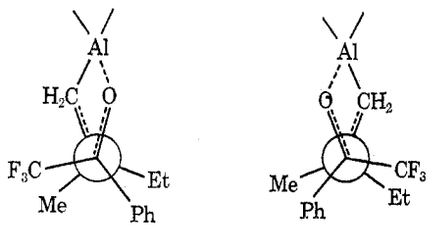
(31) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 138.

in Ia (Scheme II); thus the stereoselectivity should increase as the alkyl group changes from methyl to isopropyl (Table III). Considering that the free-energy differences among the transition states may be very sensitive to small changes in the nature of the groups which are compressed in these states, the effective sizes of the groups depend substantially on the ability of the angular and torsional strains in the cyclic transition state to minimize the van der Waals compressions.[32] Therefore the decrease in the stereoselectivity when the isopropyl is replaced by a *tert*-butyl group (Table III) might be explained supposing that the angular strains are no more able to diminish further the steric interactions among the groups which are compressed in the transition states; so the difference in free energy between Ia and IIb (Scheme II) drops down.

These suggestions seem to be confirmed by the lack of stereoselectivity in the reduction of α-tetralone, in which the phenyl group is effectively in a "frozen" conformation, both in Ia and IIb; therefore these diastereoisomeric states have very nearly the same energy.

On the basis of simple steric considerations[3,5] the reduction of trifluoromethyl phenyl ketone should lead to *R* carbinol.[33] On the contrary, opposite stereoselectivity is observed in the reduction of this ketone by (*S*)-2-methylbutylaluminum derivatives (Table I) in accordance with the data reported for the reduction by the comparable chiral Grignard reagent.[3b] Taking into account the conformational approach we have adopted, it is possible, however, to rationalize the stereochemistry of the reduction of trifluoromethyl phenyl ketone too. In fact the reacting conformations IIIa and IIIb (Scheme III) are the stablest since the

SCHEME III



$CH_2Al^{\delta+}$ is placed between the negative dipoles $C\text{–}O^{\delta-}$ and $C\text{–}CF_3^{\delta-}$.[34] However, IIIa should be reasonably the less hindered transition state, as the CF_3 is in a quasi-anti position with respect to the ethyl group, all the other interactions (Me ↔ Ph ↔ Et) being comparable both in IIIa and IIIb (Scheme III); so the *S* alcohol should be formed predominantly. In this connection it is not necessary to suppose that trifluoromethyl acts as if it were larger than phenyl group, this hypothesis being effectively incompatible with general evidence.[5]

(32) D. R. Boyd and M. A. McKervey, *Quart. Rev., Chem. Soc.*, **22**, 100 (1968).

(33) (*R*)-Trifluoromethylphenylcarbinol is configurationally related to (*S*)-methylphenylcarbinol.[5]

(34) We cannot exclude also the possibility that conformations IIIa and IIIb are further stabilized by intermolecular attractive forces between the fluorine and aluminum atoms, and these phenomena could be responsible for the relatively low extent of asymmetric reduction (Table III) in relation to a decrease of the difference between the free energies of the two diastereoisomeric states.

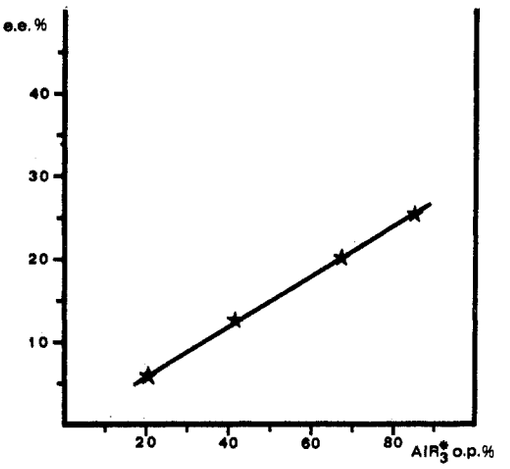
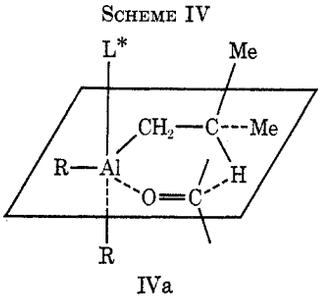


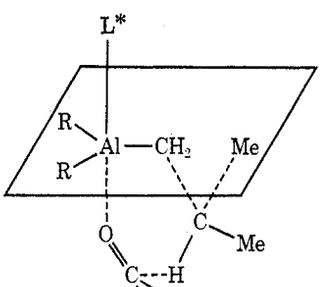
Figure 1.—Asymmetric reduction of *tert*-butyl phenyl ketone by (+)-tris[(*S*)-2-methylbutyl]aluminum: relationship between the carbinol e.e.% and aluminum alkyl optical purity.

When the optically active organoaluminum compounds are complexed with ethers the general trend of asymmetric reduction is not substantially changed, although the nature of the ligand seems to influence the stereoselectivity of the reaction (Table III). In fact, according to our previous suggestions, the ligand present in the transition state (as in IVa or IVb) should modify the relative steric interactions (Scheme IV).

SCHEME IV



IVa



IVb

The different electronegativity of aluminum atom, in relation to the basic strength of the ether employed,[25] will operate to make the cyclic transition state looser and so the mutual steric interactions will play a less important role, affecting therefore the extent of asymmetric reduction. On the other hand, the steric bulk properties of the ligand, which exerts itself a certain compression on the groups interacting in the transition states, should affect the stereoselectivity of the reaction and therefore the amount of *S* enantiomer would be expected to decrease, as a function of the bulk of the ligand, from THF to diethyl ether. These factors should act in opposition to each other, and in fact the

per cent of asymmetric reduction is greater in the presence of THF than of diethyl ether (Table III).

This conformational analysis was restricted only to the examination of the steric interactions between the alkyl phenyl ketone and the reacting 2-methylbutyl group bound to aluminum atom, although the other two optically active alkyl groups were able, in principle, to exert a further control on the stereochemistry of the reduction. The linear relationship we have observed between the per cent of enantiomeric excess of the carbinol and optical purity of (+)-tris-[(*S*)-2-methylbutyl]aluminum in the reduction of *tert*-butyl phenyl ketone (Figure 1) excludes effectively that the two unreacting optically active alkyl groups control the asymmetric reduction of ketones. This result agrees with the data, previously reported, on the reduction of methyl *tert*-butyl ketone by bis[(*S*)-2-methylbutyl]magnesium and by the corresponding Grignard reagent, reduction which occurs with the same stereoselectivity.[35]

Registry No.—α-Tetralone, 529-34-0; α-tetralol, 530-91-6.

Acknowledgments.—This work was supported by the Consiglio Nazionale delle Ricerche, Roma. The authors are indebted to Dr. E. Chiellini (Istituto Chimica Organica Industriale, Pisa) for providing a sample of (+)-(*S*)-(1-methylpropyl) ethyl ether and to Dr. C. Botteghi (E. T. H. Technisch-Chemisches Laboratorium, Zürich) for samples of (+)-(3*S*,1′*S*)-3-(1′-methylpropyl)tetrahydrofuran.

(35) H. S. Mosher and P. K. Loeffler, *J. Amer. Chem. Soc.*, **78**, 4959 (1956).

Remote Oxidation with Photoexcited Nitrobenzene Derivatives

P. C. SCHOLL* AND MICHAEL R. VAN DE MARK

Department of Chemistry, Texas A & M University, College Station, Texas 77843

Received January 19, 1973

Remote oxidation of unactivated carbon–hydrogen bonds by photoexcited nitrobenzene derivatives is described. The procedure is illustrated by the key step in the conversion of 5α-androstan-3α-ol (**3**) to 5α-androst-14-en-3-one (**6**). Introduction of unsaturation into the steroid D ring is accomplished by irradiation of the β-(*p*-nitrophenyl)propionate ester of **3** (compound **2**). As in previously reported remote oxidations utilizing benzophenone derivatives, the selectivity of the reaction is controlled by mutual orientation of the oxidizing agent and the substrate. The advantages and limitations of nitro compounds as reagents for remote oxidation are discussed.

Remote oxidation is a process in which unactivated carbon–hydrogen bonds are selectively oxidized at substrate sites remote from existing functionality.[1] Selectivity is achieved by attaching the substrate and oxidizing agent, thus mutually orienting them. The oxidation is then initiated by irradiation, and the reaction is carried out in sufficiently dilute solution that intramolecular reactions predominate. Previous examples have employed the benzophenone phototriplet as the oxidizing agent, and a common occurrence in such reactions is the formation of a new carbon–carbon bond which must then be cleaved to remove the residue of the oxidizing agent.

We have been seeking alternative remote oxidizing agents with which carbon–carbon bond formation would not be a problem, and we report here the first successful reaction with an attached reagent other than the benzophenone group.[2]

There is precedent in the literature for believing that the photoexcited aromatic nitro group would be able to abstract hydrogen from saturated carbon. Thus nitrobenzene is reduced when irradiated in "petroleum,"[3] and irradiation of 2,5-di-*tert*-butylnitrobenzene results in oxidation of one of the methyl carbons on the 2-*tert*-butyl group and reduction of the nitro group.[4]

Results and Discussion

To test the utility of the nitro function as a remote oxidizing agent, 5α-androstan-3α-yl *p*-nitrobenzoate (**1**) was first studied. Irradiation of **1** did not result in oxidation of the steroid at unactivated positions. Instead, reaction took place at the ester group to afford, after hydrolysis, the 3α and 3β alcohols, the 3 ketone, and the Δ^2 and Δ^3 olefins.

The next compound studied was 5α-androstan-3α-yl β-(*p*-nitrophenyl)propionate (**2**). It was believed that the methylene groups would decrease the reactivity of the ester function by isolating it from the nitroaromatic chromophore, and, at the same time, provide flexibility in the attachment of the oxidizing agent, a property shown to be of importance in the benzophenone reactions.[1b]

Irradiation of **2** was first carried out using a Corex filter. The reaction product was treated with iodine–acetic acid to dehydrate any tertiary alcohols, and the ester function was saponified. The nuclear magnetic resonance (nmr) spectrum of the neutral fraction thus obtained suggested the presence of 5α-androst-14-en-3α-ol (**5**) (vinyl signal at δ 5.18).[5] Hydroboration–

(1) (a) R. Breslow and M. A. Winnik, *J. Amer. Chem. Soc.*, **91**, 3083 (1969); (b) R. Breslow and S. W. Baldwin, *ibid.*, **92**, 732 (1970); (c) R. Breslow and P. C. Scholl, *ibid.*, **93**, 2331 (1971); (d) R. Breslow and P. Kalicky, *ibid.*, **93**, 3540 (1971); (e) J. E. Baldwin, A. R. Bhatnagar, and R. W. Harper, *Chem. Commun.*, 659 (1970).

(2) There are reports in which selective oxidations are achieved by means other than direct attachment of reagent and substrate. Selective radical chlorination resulted when only one end of a straight-chain substrate was exposed to chlorine dissolved in CCl_4, the other substrate end being adsorbed on a solid surface: N. C. Deno, R. Fishbein, and C. Pierson, *J. Amer. Chem. Soc.*, **92**, 1451 (1970). Reports of intermolecular oxidations which are selective at steroid position 14 have also appeared: R. Breslow, J. A. Dale, P. Kalicky, S. Y. Liu, and W. N. Washburn, *J. Amer. Chem. Soc.*, **94**, 3276 (1972); A. Rotman and Y. Mazur, *ibid.*, **94**, 6228 (1972).

(3) J. A. Barltrop and N. J. Bunce, *J. Chem. Soc. C*, 1467 (1968).

(4) D. Dopp, *Chem. Commun.*, 1284 (1968).

(5) L. Mamlok, *Bull. Soc. Chim. Fr.*, 3827 (1967).