Alkyl Metal Asymmetric Reduction. 12.[1] Optically Active Phenylalkanes from Organoaluminum Derivatives and Aliphatic Ketones

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The reaction of β-branched alkylaluminum dichloride with some aliphatic ketones has been studied in various solvents at room temperature. In benzene, the organoaluminum derivative rapidly reduces the ketone with formation of the alkoxyaluminum dichloride, which slowly alkylates the benzene to the corresponding phenylalkane. When optically active (2-methylbutyl)aluminum dichloride is used, both the carbinol from hydrolysis of the alkoxy aluminum species and the phenylalkane are optically active and of opposite absolute configuration. The overall results are also interpreted on the basis of previous findings, and a mechanism that accounts for the formation of the optically active phenylalkanes is presented.

In a recent report,[2] we have shown that alkylaluminum halides react in diethyl ether with isopropyl phenyl ketone to afford the corresponding carbinol and/or 1-phenyl-2-methyl-1-halopropane under suitable reaction conditions. Moreover, when optically active alkylaluminum derivatives are employed, conversion of the ketone to the alcohol and the halide occurs enantioselectively.[2] Continuing interest in alkylmetal asymmetric reductions has prompted us to extend our investigations on the reaction between aliphatic methyl ketones and β-branched alkylaluminum dichlorides such as isobutyl- and (*S*)-(2-methylbutyl)aluminum derivatives. In this context, we report here some interesting aspects of the dynamics and the stereochemistry of the reaction, along with a mechanistic approach to the results obtained.

Results and Discussion

The organoaluminum dichlorides used were prepared from the trialkylalane and aluminum trichloride according to literature methods.[3] The experiments were carried out at room temperature, in anhydrous hydrocarbon or ethereal solvents, by treating the organoaluminum compound with the stoichiometric amount of the ketone. We have previously found that isobutylaluminum dihalides react very slowly with isopropyl phenyl ketone to afford the corresponding reduction carbinol, which is rapidly and completely converted into the corresponding halide and alkene.[2] Contrary to this finding, isobutylaluminum dichloride reacts rather quickly with alkyl methyl ketones both in ether and in pentane. The reaction is completed within 2 h, and, upon hydrolysis, the alkylmethylcarbinol is recovered in a nearly quantitative yield: as generally observed for other cases,[2,4] neither addition nor significant enolization occurred. Moreover, at least at room temperature, no formation of the corresponding chloride or alkene is noted, even if the reaction mixture is allowed to stand for several days.

Surprisingly, when benzene is employed as the solvent (molar ratio of benzene to ketone of 5:1) and the reaction time is prolonged, the yield of the reduction product decreases progressively and new products, identified as phenylalkanes, can be detected in the reaction mixture (Scheme I, Table I). Thus, the reaction of isobutylaluminum dichloride with 2-butanone in benzene yields 2-butanol as main product after 3 h, while 2-phenylbutane

Scheme I

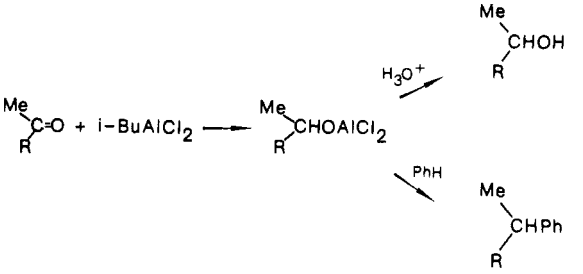

Table I. Products from Reaction between Alkyl Methyl Ketones and Isobutylaluminum Dichloride in Benzene after 24 h

ketone	products	yields, % (by GLC)
2-butanone	2-methyl-2-phenylpropane	28
	2-phenylbutane	72
3-methyl-2-butanone	2-methyl-2-phenylpropane	31
	3-methyl-2-phenylbutane	68
	2-methyl-2-phenylbutane	1
3,3-dimethyl-2-butanone	2-methyl-2-phenylpropane	24
	3,3-dimethyl-2-phenylbutane	65
	2,3-dimethyl-2-phenylbutane	11

and minor amounts of 2-methyl-2-phenylpropane are recovered after 24 h.[5] At least under the experimental conditions adopted, polyalkylated benzene compounds were not detected, and the formation of isomeric phenylalkanes was shown to be limited (Table I). In addition, it is to be noted that the formation of 2-methyl-2-phenylpropane may be prevented by removal of the isobutene, formed during the reduction of the ketone by the isobutylaluminum dichloride, at reduced pressure (350 torr). By this expedient, for example, 2-butanone quantitatively affords 2-phenylbutane.

The behavior of (2-methylbutyl)aluminum dichloride is practically analogous to that of the isobutylaluminum derivative: the reaction with 2-butanone in benzene yields 2-butanol after 2 h and yields 2-phenylbutane (53%) and

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(3) Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4792–4797.
(4) Giacomelli, G.; Menicagli, R.; Lardicci, L. *J. Org. Chem.* **1974**, *39*, 1757–1758.

(5) After ca. 12 h, from hydrolysis of the reaction mixture, the carbinol is recovered in a 38% yield together with a 60% yield of the mixture of the phenylalkanes. It is worth noting that the formation of the benzene derivatives can be accelerated from traces of free aluminum trichloride.

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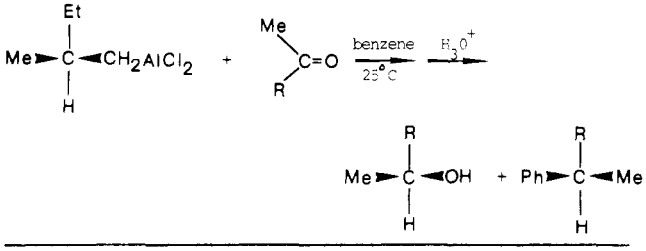
Table II. Products from Reaction between Alkyl Methyl Ketones and (S)-(2-Methylbutyl)aluminum Dichloride



R	carbinol (recovd after 3 h) [α]²⁵D (neat), deg	carbinol (recovd after 3 h) optical purity,[a] %	phenylalkane (recovd after 24 h) [α]²⁵D (c, heptane), deg	phenylalkane (recovd after 24 h) optical purity, %
Et	+0.88	5.7	−1.48 (neat)	5.1[b]
i-Pr	+0.52	9.8	−2.05 (neat)	7.0[b]
t-Bu	+0.83	10.9	−0.60 (5.96)	2.6[c]

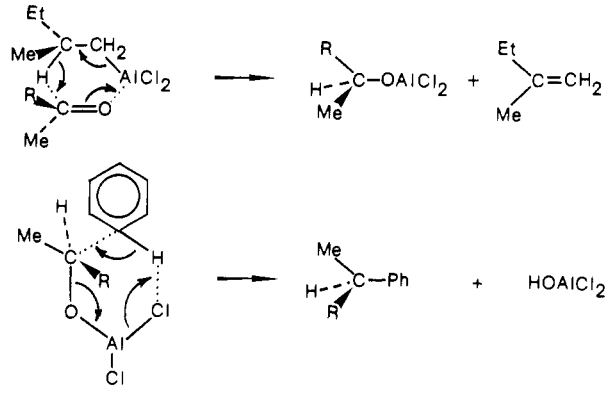
[a] See ref 4. [b] See ref 9. [c] See ref 11.

a mixture (47%) of 3-methyl-2-phenylbutane and 2-methyl-2-phenylbutane after 24 h. The formation of these last phenylalkanes probably derives from the presence of 2-methylbutenes in the reaction mixture. In fact, the treatment of 2-methyl-1-butene[6] with (2-butyloxy)aluminum dichloride (prepared by an independent route) under reaction conditions similar to those adopted for the reduction process leads, in the absence of benzene, to a mixture of 2-methyl-1-butene and 2-methyl-2-butene which are rapidly converted, in benzene, into the corresponding phenylalkanes.

Analogous to previous findings,[2,4] the reactions between alkyl methyl ketone and optically active (S)-(2-methylbutyl)aluminum dichloride occur with defined asymmetric induction phenomena. In all the cases investigated, the carbinols, recovered after 3 h, were optically active and had the absolute S configuration (Table II). We can observe that the stereoselectivity of the reduction depends upon the steric hindrance to the carbonyl carbon atom, increasing in the order of Et < *i*-Pr < *t*-Bu. In this context, it is worth noting that, apart from the case of methyl ethyl ketone, the stereoselectivity of these reductions is lower than that of the reductions of the same ketones by tris[(S)-2-methylbutyl]aluminum.[4] However, the stereoselectivity of the reduction can easily be accommodated by considerations based on the stereochemical models previously proposed.[2,4,7]

If the mixtures are allowed to stand for 24 h,[8] optically active phenylalkanes can be recovered (Table II). The results obtained show that in all the cases the phenylalkanes had the absolute R configuration,[9,10] opposite that of the carbinols from which were formally derived. Moreover, a comparison of the values of the optical purity of the phenylalkanes[9-11] with those of the optical purity of the related carbinols indicates that the conversion of the alkoxyaluminum dichloride into the benzene derivative occurs with a very high (89%) degree of inversion of configuration only in the case of 2-phenylbutane (Table II). The loss of optical purity from the carbinol to the phenylalkane increases as the steric hindrance to the asymmetric carbon atom of the carbinol increases.

Scheme II



In order to estimate the net stereospecificity of these reactions, we have examined the possibility of racemization of the products[12] during the reaction: therefore, a sample of optically active 3,3-dimethyl-2-phenylbutane was treated with ethoxyaluminum dichloride under the same conditions as those of the reduction reaction. The specific rotation of this phenylalkane remained unchanged before and after the treatment. Thus, it turns out that the loss of optical purity in the conversion of the alkoxyaluminum dichlorides into the phenylalkanes (Table II) is not to be attributed to the successive racemization of the product.

As regards the mechanism of the reaction, on the basis of previous results,[2] one may suppose that the formation of the phenylalkanes arises from a Friedel–Craft-type alkylation of benzene by an intermediate alkyl chloride formed from the alkoxyaluminum dichloride.[2] The moderate stereospecificity observed should so depend on the slow racemization of the alkyl chloride during the course of the reaction owing to the presence of significant amounts of aluminum salts.[2] This hypothesis is to be ruled out because of the lack of evidence of the formation of the alkyl chloride during the reaction. It seems likely that the phenylalkane is directly derived from the alkylation of benzene by the alkoxyaluminum dichloride itself. In the case of optically active alkoxyaluminum derivatives such an alkylation should proceed with predominant inversion of configuration. On these bases, a possible mechanism which would account for the observed stereochemistry should be based on the fast reduction of the ketone by the alkylaluminum dichloride, followed by a slow conversion of the alkoxyaluminum derivative into the phenylalkane, through a cyclic six-membered transition state in which benzene attacks the alkoxy species as a nucleophile (Scheme II). The lower stereospecificity of the alkylation observed in the cases of isopropyl and *tert*-butyl methyl ketones (Table II) may be due to the increased steric hindrance to the asymmetric carbon atom, which should hinder the back-side attack of benzene, or to the increased carbocation character of the asymmetric carbon atom. This last suggestion would account for the presence of isomeric phenyl alkanes, when more hindered ketones are also employed.

Experimental Section

Triisobutylaluminum was obtained from Fluka A. G. Co. and purified by distillation under vacuum. (+)-Tris[(S)-2-methyl-

(6) This olefin is originated from the reduction process involving (2-methylbutyl)aluminum dichloride and the ketone.
(7) Giacomelli, G.; Menicagli, R.; Lardicci, L. *J. Am. Chem. Soc.* **1975**, *97*, 4009–4012.
(8) After 3 h, the 2-methylbutenes formed were removed at reduced pressure (300 torr).
(9) Lardicci, L.; Menicagli, R. *Atti Soc. Toscana Sci. Nat. Pisa, Mem., Ser. A* **1970**, *77*, 25–39.
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(11) Giacomelli, G.; Bertero, L.; Lardicci, L. *Tetrahedron Lett.* **1981**, *21*, 883–886.
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butyl]aluminum diethyl etherate ($[\alpha]^{25}_D$ +22.28° (c 6.17, pentane)),[13] was prepared as previously described.[14] All the organoaluminum compounds were stored in sealed capillary glass vials in weighed amounts. The organoaluminum dichlorides were prepared from the trialkylalane by the redistribution with crushed anhydrous $AlCl_3$ in diethyl ether at 0 °C.[3] The solvents were commercial reagent-grade materials, purified by standard methods and redistilled under nitrogen from $LiAlH_4$ before use. GLC analyses were performed on a Perkin-Elmer 3920 B instrument with flame-ionization detectors and using 200 × 0.29 cm columns packed with 8% Carbowax 20M plus 2% KOH on 80–100-mesh Chromosorb W, while preparative GLC was carried out in a Perkin-Elmer F-21 chromatography (300 × 0.80 cm columns, 8% Carbowax 20M plus 2% KOH on 80–100-mesh Chromosorb W). ^1H NMR spectra were obtained by using a Varian A-60 spectrometer. Optical rotations were measured at the 589.6-nm sodium line with a Perkin-Elmer 142 automatic polarimeter.

General Procedure. All reactions were carried out at least in duplicate under a dry nitrogen atmosphere. In a typical small-scale reaction, a three-necked, 25-mL, round-bottomed flask was fitted with a stirring bar, a glass stopcock, a Versilic silicone cap, and a sealed angular piece of glass tubing containing 10.21 mmol of $AlCl_3$. The vessel was charged with 10 mL of ether and cooled at 0 °C, and *i*-Bu_3Al (5.11 mmol) was added from the sealed capillary glass vials. The reaction flask was then turned so that the solid $AlCl_3$ dropped into the trialkylalane solution. After a 5-min agitation, the ether was removed at reduced pressure (0.1 torr), and benzene (72.82 mmol, 6.47 mL) was injected by hypodermic syringe through the cap at the same temperature, followed by the ketone (14.56 mmol). The resulting mixture was stirred at room temperature (ca. 25 °C) for the desired time of aging. At intervals, samples of the mixture (0.4 mL) were withdrawn by a 500-μL hypodermic syringe and quenched in 10% H_2SO_4 solution (1 mL); quantitative and qualitative analyses of the reaction products were performed by GLC on the crude mixture. All products were isolated by preparative GLC, and when necessary their structures were deduced from ^1H NMR and mass spectra.

Asymmetric Reduction of Isopropyl Methyl Ketone. The following procedure is representative of all the experiments. Isopropyl methyl ketone (24.05 mmol, 2.12 g) was added rapidly at 0 °C to a benzene solution (10.7 mL) of (*S*)-(2-methylbutyl)-aluminum dichloride (25.32 mmol) in a flame-dried, two-necked 100-mL flask. A light yellow coloration developed immediately and faded slowly. After 3 h, the benzene was accurately removed at 0.1 torr, 25 mL of pentane was added, and the resulting mixture was cautiously hydrolyzed with dilute sulfuric acid, extracted with pentane, washed with a dilute $NaHCO_3$ solution, and dried (Na_2SO_4). Removal of the solvent and distillation afforded (+)-(*S*)-3-methyl-2-butanol: 2.07 g (93% yield); bp 113 °C; $[\alpha]^{25}_D$ +0.52° (neat).[4]

In an another experiment, isopropyl methyl ketone (26.08 mmol) was reacted in benzene (11.6 mL) with (*S*)-(2-methylbutyl)aluminum dichloride (27.45 mmol). After 3 h, the volatile products[15] were removed at reduced pressure (300 torr), and the reaction mixture was stirred at room temperature for additional 21 h. Hydrolysis was accomplished as above, and the organic products were extracted with pentane. Preparative GLC purification afforded 2-methyl-2-phenylbutane [NMR ($CDCl_3$,Me_4Si) δ 0.67 (3 H, t, CH_3CH_2), 1.27 (6 H, s, $(CH_3)_2C$), 1.67 (2 H, q, CH_2C), 7.30 (5 H, m, C_6H_5)] and (−)-(*R*)-3-methyl-2-phenylbutane: bp 86 °C (21 torr); $[\alpha]^{25}_D$ −2.05° (neat).[9]

Additional Experiments. 2-Methyl-1-butene (0.87 g, 12.39 mmol) was added to [(2-butyl)oxy]aluminum dichloride (12.39 mmol), prepared from 2-butanol and isobutylaluminum dichloride, and the mixture was stirred at room temperature. After 3 h, the olefin, recovered at reduced pressure, was shown to contain 23% of 2-methyl-2-butene. Another run was carried out in benzene (5.5 mL) for 24 h. After hydrolysis with dilute sulfuric acid, GLC analysis of the pentane extracts showed the presence of 2-phenylbutane (53%), 3-methyl-2-phenylbutane (15%), and 2-methyl-2-phenylbutane. (+)-(*S*)-3,3-Dimethyl-2-phenylbutane [1.95 g, 12.00 mmol; $[\alpha]^{25}_D$ + 5.30° (c 6.2, heptane)][11] was added to a benzene (1.0 mL) solution of ethoxyaluminum dichloride (12.00 mmol), prepared from anhydrous ethanol and isobutylaluminum dichloride. The mixture was stirred for 24 h at room temperature, hydrolyzed, and extracted with pentane. GLC purification yielded 1.72 g of (+)-(*S*)-3,3-dimethyl-2-phenylbutane, $[\alpha]^{25}_D$ +5.32° (c 4.81, heptane).[11]

Registry No. 2-Butanone, 78-93-3; 3-methyl-2-butanone, 563-80-4; 3,3-dimethyl-2-butanone, 75-97-8; isobutylaluminum dichloride, 1888-87-5; (*S*)-(2-methylbutyl)aluminum dichloride, 82732-01-2; benzene, 71-43-2.

(13) Giacomelli, G.; Menicagli, R.; Lardicci, L. *J. Org. Chem.* **1973**, *38*, 2370–2376.

(14) Pino, P.; Lardicci L.; Lorenzi, G. P. *Ann. Chim. (Rome)* **1958**, *48*, 1426–1437.

(15) A mixture of 2-methyl-1-butene (81%) and 2-methyl-2-butene (19%) was recovered together with traces of benzene.

Synthesis of a Modified Anthracycline: 4,6,9,11-Tetradeoxydaunomycinone

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The preparation of a tetradeoxy anthracyclinone is described. The key reaction is the cyclization of the acetylenic coumarin **10** to anthraquinone **11**. Interestingly, the related model system **12** failed to cyclize. The transformation of **11** into the desired compound **13** was effected by straightforward reactions. The key intramolecular cyclization reaction is also useful for the preparation of phthalide quinone **7**.

As a consequence of the potent biological activity exhibited by the anthracyclines, several synthetic approaches to this class of molecules have been reported.[2] While many reports describe research directed toward the synthesis of the parent compounds, an increasing number of publications has focused on the preparation of synthetic analogues. Several deoxy analogues have been synthesized.[3] Among these, the 4-deoxyanthracyclines constitute the largest class. These modified anthracyclines possess

(1) A portion of this paper has been taken from the unfinished Ph.D. thesis of John O. Pezzanite.

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