NOTE

Optically active Meerwein–Ponndorf catalyst and its use for asymmetric reductions
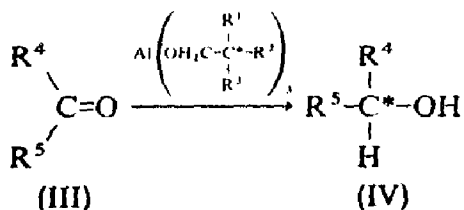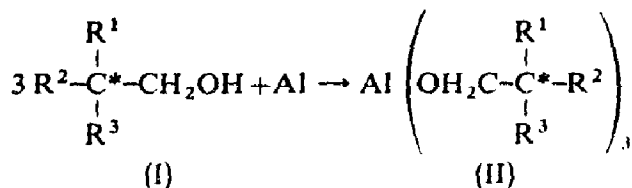
The Meerwein–Ponndorf method of reducing carbonyl groups to the alcohols is well known, as is the reverse oxidative reaction, Oppenauer oxidation, using the same aluminum alkoxides. Extensive reviews are available[1].

Baker and Linn[2] tried to reduce some unsymmetric ketones to the corresponding optically active alcohols using aluminum active alkoxide but satisfactory results were not obtained. They did not satisfactorily characterize the catalyst, aluminum tris(2-methylbutoxide), and reduction of acetophenone was not successful.

Macbeth and Mills[3] modified the Meerwein–Ponndorf method by keeping the concentration of reactive carbonyl compounds low, thus preventing undesirable side reactions, such as Tischenko or Cannizzaro reactions.

In the present work, the optically active aluminum tris(2-methylbutoxide) was prepared and characterized successfully, and used for the reduction of several ketones; the ketones were unsymmetric, and thus capable of giving optically active alcohols. The reactions may proceed as follows:

$$3 \; R^2-\overset{\overset{\displaystyle R^1}{|}}{\underset{\underset{\displaystyle R^3}{|}}{C}}{}^*-CH_2OH + Al \longrightarrow Al\left(OH_2C-\overset{\overset{\displaystyle R^1}{|}}{\underset{\underset{\displaystyle R^3}{|}}{C}}{}^*-R^2\right)_3$$

$$\text{(I)} \qquad\qquad\qquad\qquad \text{(II)}$$

$$\overset{\displaystyle R^4}{\underset{\displaystyle R^5}{}}C=O \quad\xrightarrow{\;Al\left(OH_2C-C^*-R^2\right)_3\;}\quad R^5-\overset{\overset{\displaystyle R^4}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}{}^*-OH$$
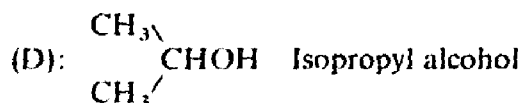
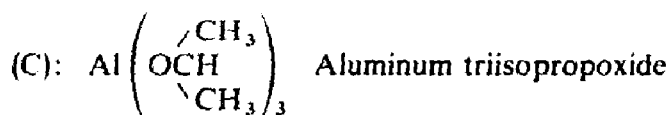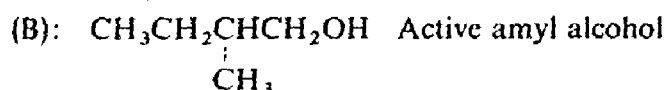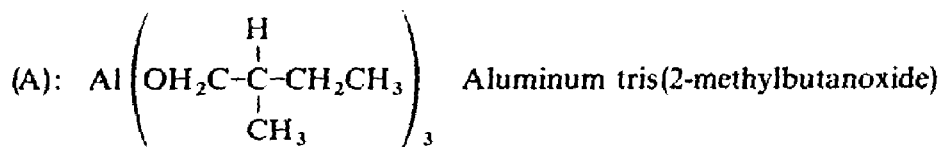$$\text{(III)} \qquad\qquad\qquad\qquad \text{(IV)}$$

where $R^1 \neq R^2 \neq R^3 =$ alkyl, aryl or H.
$R^4 \neq R^5 =$ alkyl or aryl.

That is, optically active alcohols (I) react with aluminum metal to form optically active Meerwein–Ponndorf catalysts (II). Asymmetric ketones (III) are reduced to the corresponding optically active alcohols (IV), forming a new optically active center $-\overset{|}{\underset{|}{C}}{}^*-$, by the catalyst (II).

Optically active alcohols were produced in good yields in excellent optical purity. The method has obviously advantage in the simplicity and purity over the racemic resolution methods[4]; that is, laborious resolution techniques can be eliminated and loss of the yield in multi-step processes is avoided.

The following three combinations of alcohols and catalysts were used.

(1) Optically active catalyst (A) + Optically active solvent (B)
(2) Optically inactive catalyst (C) + Optically active solvent (B)
(3) Optically active catalyst (A) + Optically inactive solvent (D)

$$
\text{(A):}\quad Al\left(OH_2C\text{-}\underset{\underset{CH_3}{|}}{\overset{\overset{H}{|}}{C}}\text{-}CH_2CH_3\right)_3 \quad \text{Aluminum tris(2-methylbutanoxide)}
$$

$$
\text{(B):}\quad CH_3CH_2\underset{\underset{CH_3}{|}}{CH}CH_2OH \quad \text{Active amyl alcohol}
$$

$$
\text{(C):}\quad Al\left(O\underset{\underset{CH_3}{\backslash}}{\overset{\overset{CH_3}{/}}{C}}H\right)_3 \quad \text{Aluminum triisopropoxide}
$$

$$
\text{(D):}\quad \underset{CH_3/}{\overset{CH_3\backslash}{}}CHOH \quad \text{Isopropyl alcohol}
$$

In the light of the results of the preliminary investigations, the experiments reported here were carried out exclusively in the reaction system (1). In system (2), the alcohol part of the aluminum catalyst underwent the alcohol exchange reaction, as Baker and Linn[2] also found. In the system (3) the optical purity of the product was not as good as that obtained in the system (1), although the Meerwein–Ponndorf reduction may be successfully carried out in non-alcoholic solvents, such as hydrocarbons[1].

The present method is thus essentially a combination of Baker and Linn's[2] and Macbeth and Mills'[3] methods.

Configurational relation between the alcohols in the aluminum catalyst and the products, optical inversion of some cyclic ketones[5], reductions of the precursors of steroid and alkaloid, and application of the method to the synthesis of natural products are now under investigation.

Experimental

All experiments were carried out in duplicate.

Preparation of the optically active catalyst

Aluminum powder, guaranteed reagent, was used without any further purification, rather than the aluminum wire or foil usually used.

Active amyl alcohol, or (−)2-methylbutanol-1 was a commercial product, and distilled before use, b.p. 128°, d_4^{20} 0.816, n_D^{25} 1.409, $[\alpha]_{589\,m\mu}^{25} = -10.13$, $[\alpha]_{436\,m\mu}^{25} = -19.70$.

Aluminum triisopropoxide was a commercial preparation. The aluminum content was checked by analysis, and the compound was more than 98 % pure.

Measurement of the optical rotation was made with a manual spectrophotometric polarimeter, Hitachi EPU Type 2, at 589 mμ and 436 mμ, corresponding to the Na D_2 line and one of the Hg lines, respectively.

Method 1. To 27 g (1 mole) of powdered aluminum in a 500 ml-round-bottomed flask, about 100 mg of mercuric chloride crystals were added. An efficient reflux condenser, a dropping funnel, and a thermometer were attached to the flask. Active amyl alcohol, 264 g (3 moles), was added to the flask dropwise, preferably initially on the crystals of mercuric chloride, and the flask was gently heated. Vigorously reaction took place, and the rate of addition and the heating had to be carefully controlled. After addition of all the active amyl alcohol, the refluxing was continued for about 12 h. Although the reaction was not complete, at this point the residual unreacted active alcohol was removed by distillation under reduced pressure. Ether or chloroform, 100 ml and three 50 ml portions, was added to the residue and optical active aluminum tris(2-methylbutoxide) was extracted four times. Solvents were distilled from the combined extracts to leave the catalyst as white powder. In this method the yield of the catalyst was not high, usually about 50 %, and purification was difficult (Method 2, below, was used to obtain and characterize the pure catalyst), but for the purposes of asymmetric reduction the impure catalyst obtained by this method was satisfactory.

Method 2. The method is essentially the alcohol exchange reaction, a secondary alcohol, isopropyl alcohol, being replaced by a primary alcohol, active amyl alcohol.

In a 500-ml-round-bottomed flask, were placed 88 g of aluminum triiso-propoxide (1 mole) and 300 g (excess) of active amyl alcohol, a reflux condenser and a thermometer were fitted, and the mixture was refluxed. When the alcohol began to boil the temperature of the vapor was about $92°$, and as the alcohol exchange reaction proceeded, the temperature fell gradually. When it reached the boiling point of isopropyl alcohol, this alcohol was slowly distilled out, about 6 h being needed for removal of the theoretical amount of the alcohol. The excess active amyl alcohol was removed under reduced pressure, to leave, as a white powder, almost pure optically active aluminum tris(2-methylbutoxide), m.p. 152–154° (dec.), $[\alpha]^{20}_{589\,m\mu} = +5.10$ (in 10% chloroform), $[\alpha]^{20}_{436\,m\mu} = +15.20$ (in 10% chloroform). Yield 98.5 %. (Found: Al, 9.78. $C_{15}H_{33}AlO_3$ calcd.: Al, 9.37 %.)

Water reacted with this alkoxide to give active amyl alcohol, which had retained all its optical activity.

Reduction of ketones

Reduction of methyl ethyl ketone. To 96 g of active aluminum tris(2-methyl-butoxide) in a 300 ml-round-bottomed flask, was added part of 88 g of active amyl alcohol, to give a suspension. A mixture of the rest of the active amyl alcohol with 72 g of methyl ethyl ketone was added dropwise to the heated contents of the flask. After 3 h refluxing the alcohol formed was carefully distilled out. Methylethylcarbinol, b.p. 100°, $[\alpha]^{20}_{589\,m\mu} = +13.08$, $[\alpha]^{20}_{436\,m\mu} = +89.63$, $d^{20}_4 = 0.800$, $n^{20}_D = 1.391$. Yield 70 g (94.6 %). (Found: C, 64.39; H, 13.82. $C_4H_{10}O$ calcd.: C, 64.86; H, 13.51 %.)

When the reduction was carried out by the system (3), the product showed lower optical rotation; $[\alpha]^{20}_{589\,m\mu} = +1.10$.

Reduction of acetophenone. The reduction procedure was the same as the case of reduction of methyl ethyl ketone except that the reflux time was 10 h. In this particular case the boiling points of the reactant, acetophenone, and the product, methylphenylcarbinol, are very close to each other (about 202°), and separation by distillation is difficult. Consequently, the product and the starting material were

distilled off together, and a 10% aqueous solution of (2,4-dinitrophenyl)hydrazine was added to precipitate all unreacted ketone. The product alcohol was extracted from the precipitate with ether, the extract was dried with anhydrous sodium sulfate, the ether was removed by distillation, and the alcohol was distilled under reduced pressure. [A separation was also carried out by another method in which the mixture of the reduction product and the starting material was cooled to near 5°, at which acetophenone (m.p. 20°) crystallized out. It was filtered off, but the residual alcohol was impure]. Methylphenylcarbinol, b.p. 202°, $[\alpha]_{589 \, m\mu}^{20} = -0.44$, $[\alpha]_{436 \, m\mu}^{20} = -1.54$, $d_4^{20} = 1.012$, $n_D^{20} = 1.531$. Yield 98 g (80.33%). (Found: C, 78.58; H, 8.01. $C_8H_{10}O$ calcd.: C, 78.68; H, 8.18%.)

Reduction of 3-methylcyclohexanone. 3-Methylcyclohexanone was also reduced with the optically active catalyst by the method described above, and optically active 3-methylcyclohexanol was obtained in 35% yield. 3-Methylcyclohexanol, b.p. 175–176°, $[\alpha]_{589 \, m\mu}^{20} = +0.36$, $[\alpha]_{436 \, m\mu}^{20} = +0.61$, $d_4^{20} = 0.874$, $n_D^{20} = 1.445$. This compound has not yet been well characterized.

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