171. Regioselective Discrimination of Antipods in a Catalytic Asymmetric Transformation

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(26. V. 76)

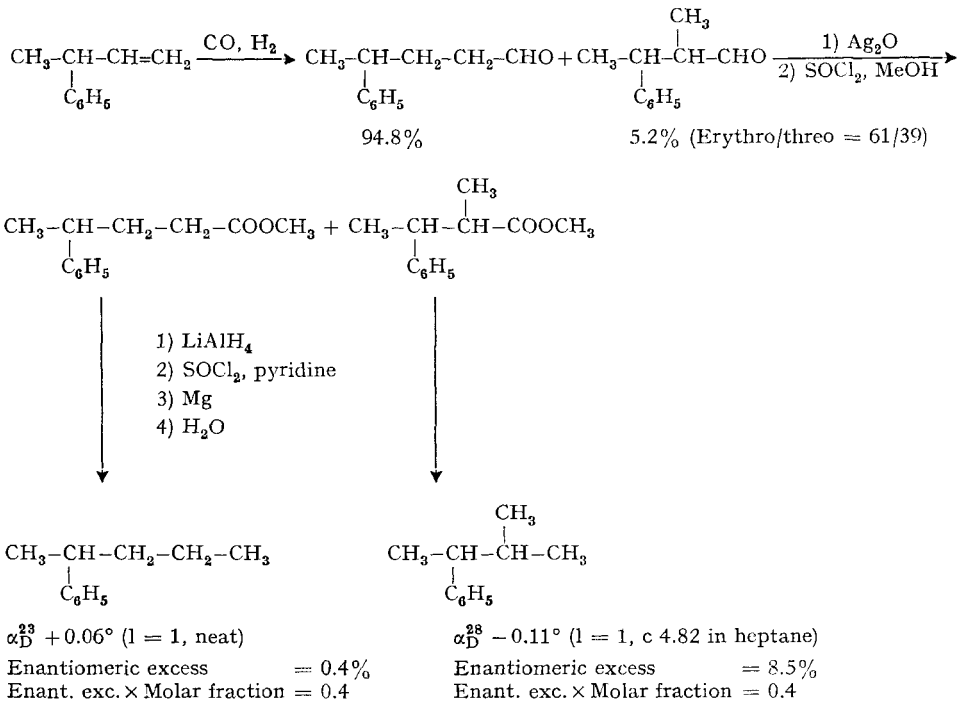
Summary. In the hydroformylation of racemic 3-phenyl-1-butene in the presence of an asymmetric rhodium-catalyst, different regioselectivities have been observed for the two enantiomers, as indicated by the optical activity of the products.

It is well known that by partial reaction of racemic substrates with optically active agents or with non chiral agents in the presence of optically active catalysts, a kinetic resolution of the racemates and the simultaneous synthesis of optically active compounds can be achieved [1]. This phenomenon, indicated in some cases as stereoelection [2], appears as an extreme case in enzymatic reactions, in which only one enantiomer can be transformed and complete resolution can be achieved [3]. However, if stereoelectivity is not complete, no optically active products are obtained when the reaction is brought to completion.

When an asymmetric reaction gives rise to more than one product, different reactivities can in principle be offered by two antipods, and optically active compounds can be obtained in this case, even after complete conversion.

In order to test the actual possibility of this type of asymmetric transformation, racemic 3-phenyl-1-butene was hydroformylated at atmospheric pressure in the presence of hydridocarbonyltris(triphenylphosphine)rhodium and (–)-DIOP [4], at 50°. A conversion higher than 99% was obtained in 30 hours, and the product consisted of 4-phenylpentanal (94.8%) and 2-methyl-3-phenylbutanal (5.2%, *erythro*/*threo* = 61:39). A considerably different ratio between the isomeric aldehydes (83% and 17% respectively) has been obtained by hydroformylation of the same substrate with rhodium supported on alumina as the catalyst [5]; the epimeric composition of the 2-methyl-3-phenylbutanal, however, was the same in both cases, indicating that it is mainly controlled by the asymmetric carbon atom present in the substrate. After oxidation of the products to the corresponding acids, and conversion of the acids to methyl esters (see *Scheme*), a separation was performed by rectification. Pure methyl 4-phenylpentanoate and a fraction containing both *erythro* and *threo* methyl 2-methyl-3-phenylbutanoate have been isolated. Both products were converted to the corresponding hydrocarbons by consecutive treatments with lithium-aluminium hydride, thionyl chloride, magnesium, and water, in order to eliminate the asymmetric centre formed in the hydroformylation, and to obtain compounds reported in the literature in the enantiomerically pure form[1]).

[1]) $\alpha_D^{23} - 15.00°$ (l = 1, neat) [6] and $\alpha_D^{28} = -23.23°$ (l = 1, neat) [7] are given respectively for enantiomerically pure 2-phenylpentane and 2-methyl-3-phenylbutane.



The resulting 2-phenylpentane had (*S*)-chirality [8] and 0.4% enantiomeric excess[2]). 2-Methyl-3-phenylbutane on the other hand showed (*R*)-chirality [7] and 8.5% enantiomeric excess[2]). As expected the two final products have opposite chiralities, and the product between enantiomeric excess and molar fraction is the same in both cases, within the limits of experimental errors. Thus the two optical activities show complementary values, and reveal the different regioselectivity of the hydroformylation for the two enantiomeric olefins: at the position 2, 5.6% formylation can be calculated for the (*R*) antipod *vs.* 4.8% for the (*S*) antipod. The above result suggests that asymmetric induction in the hydroformylation, or similar asymmetric additions to prochiral olefins, can be controlled not only by enantioselectivity (preferential attack at one prochiral face) but also by regioselectivity (different rate of attack at two different positions on one or the other prochiral face). In fact, an analogous regioselective discrimination is possible for the two faces of a prochiral olefin as well.

Experimental. – All the products were identified by combined VPC./MS. (*Perkin-Elmer* 990 gas chromatograph, *Hitachi* RMU-6L mass spectrometer). Quantitative determinations were made on the gas-chromatograms. The separation of the esters was performed with a spinning band distillation column (*Perkin-Elmer* 251) and the preparative VPC. purification on a *Perkin-Elmer* F21 gas chromatograph. Optical activities were measured with a *Perkin-Elmer* 141 digital polarimeter.

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[2]) No deviation has been assumed between optical purity and enantiomeric purity, as solutions of hydrocarbons can be considered ideal.

Hydroformylation reaction. 10 g (75 mmol) of 3-phenyl-1-butene, from the *Wittig* reaction between hydratropaldehyde and methylene-triphenylphosphorane, 185 mg (0.2 mmol) of $HRh(CO)(PPH_3)_3$, and 200 mg (0.4 mmol) of (–)-DIOP [4] in 80 ml benzene, placed in a flask connected with a gasometer under 1 atm of carbon monoxide and hydrogen in equimolar ratio, were heated at 50° and vigorously stirred until gas absorption ceased (*ca.* 30 h). The analysis of the mixture indicated that residual 3-phenyl-1-butene was less than 1%, and the product consisted of *erythro*-2-methyl-3-phenylbutanal (3.2%), *threo*-2-methyl-3-phenylbutanal (2%), and 4-phenylpentanal (94.8%), in the order of elution on carbowax 20 M [9].

Determination of the optical activities. The crude product from the hydroformylation was oxidized with alkaline Ag_2O [10] and the resulting mixture of acids esterified by treatment with one equivalent of $SOCl_2$ in methanol. 50 g of the methyl esters, result of a number of similar runs, were rectified at reduced pressure. In order to avoid cross fractions of 2-methyl-3-phenylbutanoate and 4-phenylpentanoate, some methyl 4-phenylbutanoate, having an intermediate boiling point, was added to the mixture. *Erythro-* and *threo*-2-methyl-3-phenylbutanoate were collected in one fraction, b.p. 110–120°/8–10 Torr, along with an equal amount of 4-phenylbutanoate. A fraction of pure 4-phenylpentanoate, b.p. 123–124°/8 Torr, was treated with $LiAlH_4$ in ether. The resulting alcohol, by reaction with $SOCl_2$ in pyridine, afforded the corresponding chloride. Reaction with magnesium in ether and successive hydrolysis of the *Grignard* solution gave 2-phenylpentane, b.p. 188–190°, with an overall yield of 70%. For the hydrocarbon obtained, the rotation $\alpha_D^{23} + 0.06°$ ($l = 1$, neat) was measured, corresponding to a prevalence of (*S*) configuration [8] and 0.4% enantiomeric excess [6].

The epimeric mixture of 2-methyl-3-phenylbutanoate was converted to 2-methyl-3-phenylbutane by analogous procedure, and the hydrocarbon was isolated by prep. GC. The rotation of the collected product, $\alpha_D^{28} = -0.11°$ ($l = 1$, $c = 4.82$ in heptane), indicated a prevalence of (*R*) configuration and 8.5% enantiomeric excess [7].

We thank the *Schweizerischen Nationalfonds zur Föderung der wissenschaftlichen Forschung* for the financial support of this investigation.

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