Asymmetric Reduction of Trifluoromethyl Ketones by Actively Fermenting Yeast

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Summary Optically active (*R*)-cyclohexyl-, (*R*)-phenyl-, (*R*)-α-naphthyl-, and (*R*)-β-naphthyl-trifluoroethanols have been obtained in good chemical, and high optical, yields, by reduction of the corresponding ketones by actively fermenting yeast.

SYNTHESES of chiral carbinols containing the trifluoromethyl group are of interest especially for their practical utility, and optically active 2,2,2-tri-fluoroethanols are commonly used as solvents in n.m.r. spectroscopy for the determination of the enantiomeric purity and absolute configuration of a variety of chiral substances.[1] More recently, it has been shown that the same solvents can also be used to induce asymmetric syntheses of optically active compounds.[2]

Enantiomers of chiral trifluoroethanols are usually obtained by resolution of the racemates[3] or by asymmetric reductions of the corresponding trifluoromethyl ketones with chiral chemical reagents.[4] Syntheses of these compounds *via* the stereoselective reduction of the carbonyl substrates by enzyme–coenzyme systems, *i.e.* by a procedure which is well known to effect asymmetric syntheses and resolutions of chiral alcohols,[5] have not yet reported.

We have now investigated the reduction of cyclic aliphatic (**1a**) and aromatic (**1b**—**e**) trifluoromethyl ketones by actively fermenting fresh commercial baker's yeast.

$RC(:O)CF_3$ (**1**) $RCH(OH)CF_3$ (**2**)

a; R = cyclohexyl
b; R = Ph
c; R = α-naphthyl
d; R = β-naphthyl
e; R = mesityl

In a typical experiment the carbonyl compound (5 mmol) was added to a fermenting yeast (35 g)–sucrose (40 g)–water (190 ml) suspension and the mixture kept at 32 °C. After 2 days, a fresh fermenting yeast–sucrose suspension was added. After a further day g.l.c. analysis showed > 80% reduction for the ketones (**1a**—**d**), while attempted reduction of (**1e**) led to unchanged starting material only. The fermentation mixture was then steam distilled until 2 l of distillate had been collected. After 'salting out' with NaCl, ether extraction of the distillate, followed by evaporation gave the crude alcohol in good chemical yields (70—80%). The alcohols were purified to remove unchanged ketones by column chromatography on silica and fractional crystallization or distillation under reduced pressure.

The chemical yields obtained, together with the results reported in the Table, indicate that the reductive yeast fermentation of trifluoromethyl ketones offers a very simple route to optically active trifluoroethanols. In particular, the present enzymic approach is the most convenient single-step process for preparing optically pure 1-cyclohexyl- (**2a**), 1-(α-naphthyl)- (**2c**), and 1-(β-naphthyl)-2,2,2-trifluoroethanol (**2d**) with sufficient optical purity to be used as chiral media in n.m.r. spectroscopy.[6] These results clearly show that the enzyme processes, when operating on compounds having the trifluoromethyl substituent, may exhibit the same high optical yields which characterizes enzymic reductions of natural substrates.

Also, from the Table, optically active alcohols with the same (*R*) configuration at the chiral carbon atom have been obtained, independently of whether alicyclic (**1a**) or aromatic (**1b**—**d**) ketones were used. The present results can be correlated with those reported, under similar circumstances, for the unfluorinated alcohols. In particular, asymmetric reductions of methylalkyl and methylaryl ketones by actively fermenting yeast, have been proved to yield optically active ethanols with the (*S*) absolute configuration at carbon,[7] *i.e.* alcohols with the same chirality as derivatives (**2a**—**d**).† Nevertheless, any comparison of the trends in stereoselectivity between our results and those reported for methyl ketones[7] is, at present, difficult, because of the limited variety of substrates examined and because of the lack of knowledge on carbonyl reductase enzyme systems,[6] which may control the steric course of reductions of (**1a**—**d**) by fermenting yeast *in vivo*.

TABLE

Asymmetric reduction of trifluoromethyl ketones by actively fermenting yeast

Alcohol	$[\alpha]_D^{25}$/°	Absolute configuration	% Optical purity
(**2a**)	+17·7[a]	(*R*)[b]	>99[b]
(**2b**)	−18·1[c]	(*R*)[d]	44[d]
(**2c**)	−17·1[e]	(*R*)[f]	66[f]
(**2d**)	−19·1[g]	(*R*)[h]	60[h]
(**2e**)	—	—	—

[a] *c* 7·9, chloroform. [b] The absolute configuration and the optical purity of (**2a**) were established by comparison with the observed rotation of the 1-cyclohexyl-2,2,2-trifluoroethanol, $[\alpha]_D^{25}$ +17·8° (chloroform), obtained by stereospecific hydrogenation of optically pure (*R*)-(−)-2,2,2-trifluoro-1-phenyl-ethanol. [c] Pure liquid. [d] Based on the reported absolute configuration and maximum rotation of optically pure 2,2,2-trifluoro-1-phenyl-ethanol, ref. 5. [e] *c* 10·2, ethanol. [f] Based on the reported absolute configuration and maximum rotation of optically pure 2,2,2-trifluoro-1-(α-naphthyl)-ethanol, ref. 4. [g] *c* 9·2, chloroform. [h] Based on the reported absolute configuration and optical purity of partially resolved 2,2,2-trifluoro-1-(β-naphthyl)-ethanol, W. H. Pirkle and S. D. Beare, *J. Amer. Chem. Soc.*, 1967, **89**, 5485.

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† The (*R*)-trifluoroethanols (**2a**–**d**) are configurationally related to the corresponding (*S*)-ethanols.

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