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Microbial and homogenous asymmetric catalysis in the reduction of 1-[3,5-bis(trifluoromethyl)phenyl]ethanone

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Abstract—Two complementary approaches for the enantioselective reduction of 1-[3,5-bis(trifluoromethyl)phenyl]ethanone **1** are described and compared: microbial versus asymmetric reduction of ketones through asymmetric hydrogen transfer. Among the various microorganisms screened, *Lactobacillus kefir* and *Aspergillus niger* reduced ketone **1** to the corresponding (*R*)-alcohol (*R*)-**2**. The (*S*)-alcohol (*S*)-**2** was obtained by reduction of **1** using homogenous asymmetric catalysis. The configuration of the alcohol in both the biocatalysis and hydrogen transfer approaches was controlled by the choice of the enzyme and by the configuration of ligands, respectively. Both enantiomers were obtained in high yield and ee.

1. Introduction

The synthesis of chiral secondary alcohols via the catalytic reduction of the corresponding prochiral ketones is one of the key transformations in the asymmetric organic synthesis. Only a few major methods have appeared over the past two decades; among them are the enantioselective reductions with molecular hydrogen, enantioselective reduction with modified hydrides, enantioselective hydrogen transfer and biocatalysis. Biocatalysis and enantioselective hydrogen transfer are two complementary methodologies frequently used in our laboratory. Biocatalysis is today commonly used in organic synthesis. Its benefits are in an efficient and selective catalysis, including chemoselectivity, regioselectivity, diastereoselectivity and enantioselectivity. Moreover, the biocatalysts accept a broad range of 'unnatural' substrates; they act under mild reaction conditions and are biodegradable and thus environmentally friendly. Enzymes that catalyze oxidation–reduction are cofactor dependent alcohol dehydrogenases.

Substrates commonly reduced by oxidoreductases, either isolated enzymes or whole microorganisms, are β-ketoesters[1] and β-diketones,[2] then ketothioacetals[3] and related compounds, aliphatic ketones[4] and aldehydes,[5] cyclic[6] and polycyclic ketones[7] and carbon–carbon double bonds.[8] Stereoselective reductions of the carbonyl compounds by bakers' yeast (*Saccharomyces cerevisiae*) are one of the most explored biotransformations.[9–11]

Enzymatic and microbial reductions of the alkyl aryl ketones proceed in the majority of cases according to Prelog's rule[12] generating alcohols in the (*S*)-configuration. The enzyme transfers the pro-(*R*) hydrogen of the cofactor to the *re*-face of a ketone. The majority of enzymes such as HLADH and microorganisms such as bakers' yeast, *Geotrichum*, *Curvularia* or *Thermoanaerobium* follow this rule, while only a few microorganisms (*Lactobacillus*, *Mucor* and *Pseudomonas*) have been described to possess enzymes of the opposite specificity, that is, anti-Prelog's specificity.

Acetophenones and their derivatives are generally poor substrates for alcohol dehydrogenases. Although they are reduced with high enantioselectivities, the yields are generally low. However, electron withdrawing groups adjacent to a ketone moiety increase their reactivity.[13–17] The examples of microbial reductions of aromatic trifluoromethyl ketones,[18] α-ketoacids and α-ketoesters,[19] β-ketoesters[20] and imidazoyl[21] ketones have been described.

Abbreviations: ADH, alcohol dehydrogenase; ATCC, American Type Culture Collection; BY, bakers' yeast; DMAP, dimethyl-amino-pyridine; DSMZ, Deutsche Sammlung fur Microorganismen und Zellen; HLADH, horse liver alcohol dehydrogenase; $NAD(P)^+$, nicotinamide adenine dinucleotide (phosphate).

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On the other hand, asymmetric hydrogen transfer from a hydrogen donor is an oxido-redox process catalyzed by an organometallic complex. One of the most efficient asymmetric catalysts developed by Noyori[22] contains a monotosylated chiral diamine as the ligand associated to a ruthenium complex. This system was shown to be very efficient, enantioselective and independent of the substrate. The mechanism of hydrogen transfer has been described by Noyori.[23] The monotosylated chiral diamine and the ruthenium complex form an active catalyst with 18 electrons, which loses two electrons in the presence of a base. The 16 electron complex is then hydrogenated by the donor, generally 2-propanol. This active catalyst is finally able to reduce the aromatic ketone via a six-centre mechanism.[24] Both, 18- and 16-electron complexes have been isolated and their structures have been determined by X-ray.[23a] The results confirmed the hypothesis of the reduction by hydrogen transferred from ruthenium and not the metal alcoholate as in the case of Meerwein–Ponndorf–Verley reduction. The amino group is necessary for efficient catalysis by complexing the carbonyl group of the substrate. The catalytic system described has been efficiently employed in reduction of various aromatic ketones.[22]

We have applied two of the above described methodologies in the reduction of 1-[3,5-bis(trifluoromethyl)phenyl]ethanone **1**. Commercially available oxido-reductases, as well as microbial strains expressing these activities were screened. On the other hand, numerous chiral ligands associated to the ruthenium-*p*-cymene complex were screened under the conditions of homogenous asymmetric catalysis. Our objective was to evaluate the diversity of our strain collection and of the (per)fluorosulfonyl-diamine ligands in the reduction and secondly, to obtain the alcohol of (*R*)-configuration.

1-[3,5-Bis(trifluoromethyl)phenyl]ethanone **1** is a key precursor of (*R*)-1-[3,5-bis-(trifluoromethyl)phenyl]ethanol (*R*)-**2**, a sub-structure of the tachykinin NK_1 receptor antagonist L-754030, a potent anti-depressant as shown in Figure 1. Its structure is closely related to the structure of MK869, shown recently to be efficient in patients with major depressive disorder.[25]

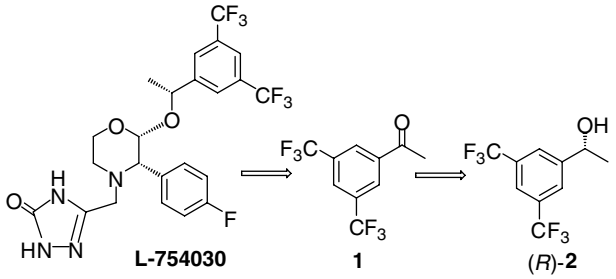

Figure 1.

2. Results and discussion

2.1. Bio-reductions

A screening of commercially available alcohol dehydrogenases (HLADH, YADH, BYADH and *Lactobacillus kefir* ADH) in the reduction of **1** was performed under different pH conditions, cofactor concentration, cofactor regeneration system and the addition of an organic cosolvent. The substrate concentration was kept constant at 5 mg/ml (20 mM). Under all conditions assayed only HLADH and *L. kefir* ADH showed activity and transformed **1** in a very moderate yield, but with 100% ee into the alcohol **2** (Fig. 2). Both enzymes reduced **1** but with the opposite enantioselectivity. While HLADH gave the (*S*)-enantiomer, *L. kefir* ADH gave an anti-Prelog's configuration, that is, the *R*-alcohol. Product configurations and the enantioselectivity of the enzymatic reductions were determined by a chiral GC comparison of the reduction products with the authentic samples.

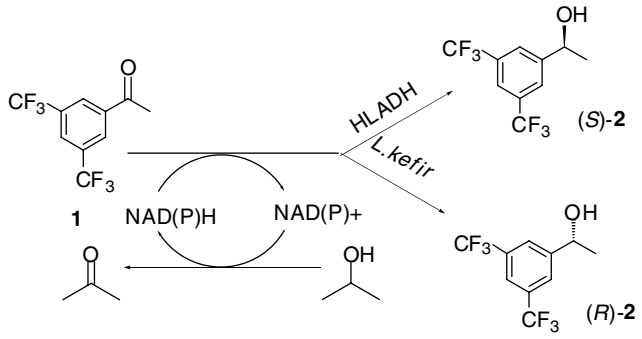

Figure 2.

The results are summarized in Table 1. A little activity was obtained without the recycling of the cofactor. When a secondary alcohol such as 2-propanol or cyclopentanol was used, the reduction was more efficient. The secondary alcohol has a dual role: first it serves to recycle the cofactor and secondly it enables better solubility of the substrate in the aqueous medium. However, by increasing the concentration of 2-propanol added, the yield of reduction decreased slightly. As the product of 2-propanol oxidation is acetone, it could possibly act as a competitive substrate of the dehydrogenase. To check this possibility, the cofactor concentration was increased for 35% (from 2 to 2.7 mM) and we observed a 50% increase in the yield of reduction. Very likely, both phenomena are taking place, that is, a substrate competition and a cofactor depletion, but it was not investigated further.

Table 1. Reduction of **1** (20 mM) with HLADH and *L. kefir* ADH

ADH	NAD(P)H (mM)	2-Propanol (μl)	Time (h)	GC yield (%)	ee (%)
L. kefir	0.2	2.5	48	15	>99 (*R*)
HLADH	2	100	48	20	>99 (*S*)
HLADH	2	25	44	24	>99 (*S*)
HLADH	2.7	100	66	49	>99 (*S*)
HLADH[a]	1	100	72	0	—
HLADH[b]	1	100	72	0	—

Conditions: 0.1 M phosphate buffer pH 7.8, 4.4–5 U/ml of ADH at 30 °C and 1300 rpm.
[a] Reaction in *n*-hexane.
[b] Reaction in acetonitrile.