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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.
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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.

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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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.

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.

Although the alcohol obtained under all conditions is enantiomerically pure, the yield is rather low. According to the literature data, the rate of enzymatic reduction can be enhanced in organic–aqueous biphasic media.[26] Reactions performed with **1** as a substrate and in the phosphate buffer–hexane medium did not give any product. In the presence of a water miscible solvent, such as acetonitrile, no product was obtained either. On the other hand, the use of organic solvents instead of buffer media can control the stereochemistry of enzymatic reduction.[13,27] Unfortunately, neither HLADH nor *L. kefir* ADH showed any activity in pure *n*-hexane or acetonitrile under assayed conditions.

These screening results revealed that *L. kefir* ADH is capable of selectively reducing **1** into the desired (*R*)-alcohol. However, the purified enzyme was not very stable in solution and we observed a loss of activity when storing the enzyme even at −80 °C. *L. kefir* is a lactic bacterium frequently used in food biotechnology. All further experiments were performed with the biocatalyst obtained by growing *L. kefir* DSM 20587. The advantage of using the whole cells instead of the isolated enzyme is in its ability to perform the reactions without the external addition of cofactors. This makes the whole procedure much easier. Initial experiments were performed with 5 mM **1** and the enantioselectivity of the microbial enzymatic system was confirmed when compared to isolated enzyme. 5 mM (1.2 g/l) **1** was completely transformed into the (*R*)-alcohol within 16 h with excellent enantioselectivity (ee >99%). The concentration of the biocatalyst used in these experiments was 20–24 g/l of dry cell mass. Higher concentrations of ketone seemed to inhibit the enzyme. For example, 100 mM **1** gave 13% of transformation in 16 h while 200 mM **1** gave only 2% under the same conditions (Table 2).

Table 2. Reduction of **1** with *L. kefir* cells

1 (mM)	**1** (g/l)	GC yield (%) (16 h)	GC yield (%) (96 h)
5	1.2	100	—
10	2.4	77	100
20	4.8	31	69
50	12	13	51
100	24	13	51
200	48	2	31

The kinetics of reductions catalyzed by *L. kefir* are presented in Figure 3. The reaction reaches a plateau at ca. 85–90% of conversion. The addition of the biocatalyst does not influence the conversion; nor does the addition of NADPH or 2-propanol for recycling the cofactor. We suspect the alcohol formed to inhibit the enzyme. However this is the subject of our ongoing study and will be reported elsewhere.

Twenty other strains were screened for the alcohol dehydrogenase activity, but only *Aspergillus niger* cells showed activity with **1** as the substrate. The activity was 10-fold lower than the activity of *L. kefir* and the enantiomer obtained has the (*R*)-configuration according to the anti-Prelog's rule (results not shown).

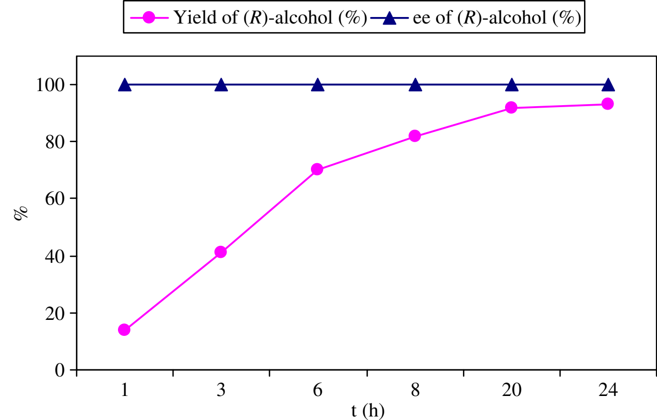

Figure 3. *L. kefir* catalyzed reduction of **1**.

2.2. Homogenous asymmetric catalysis

According to the synthesis patented by Merck,[28] the (*R*)-alcohol is available through the asymmetric reduction of **1** by using (*S*,*R*)-1-amino-2-indanol as the chiral ligand associated to $[Ru(p\text{-cymene})Cl_2]_2$. The described catalytic system allowed us to obtain the (*R*)-alcohol in an excellent yield and high enantiomeric excess.

We have prepared and screened numerous chiral ligands in the reduction of **1** (Fig. 4). The ligands used in this study were prepared by mixing a diamine with one equivalent of the corresponding chlorosulfonyl compound in dichloromethane.

1 → (*S*)-**2**
Ligand + $[Ru(p\text{-cymene})Cl_2]_2$
HCO_2H/NEt_3, 20 °C
1/ Ru / L = 100/1/1
[**1**] = 2 M

Figure 4. Reduction of **1** through homogeneous catalysis.

First, the perfluorosulfonylated ligands were screened in a formic acid/triethylamine system. This was chosen based on the previously studied reduction of acetophenone.[29] Note that the absolute configurations of the ligands are (*S*,*S*) and as a consequence the product obtained is the (*S*)-alcohol. As the desired product is the (*R*)-alcohol, it could be easily obtained with the corresponding (*R*,*R*)-1,2-diamine as the ligand. Indeed, in the case of acetophenone, the asymmetric reduction using (*S*,*R*)-1-amino-2-indanol afforded (*R*)-phenylethanol[30] and, with (*R*,*S*)-1-amino-2-indanol, (*S*)-phenylethanol[30] was obtained. Table 3 summarizes the results of the reduction of BTA with the ligands prepared in this study.

The results indicate that none of the cyclohexane diamine-based ligands **3**–**5** (entries 1–3) were efficient when compared to the amino alcohol used by Merck that gave 90%

Table 3. Reduction of **1** with perfluorosulfonylated ligands

Entry	Ligand	Time (h)	GC yield (%)	ee (%) (config)
1	$NHSO_2CF_3$, NH_2 **3**	24	100	22 (*S*)
2	$NHSO_2$–3,5-$(CF_3)_2C_6H_3$, NH_2 **4**	24	96	57 (*S*)
3	$NHSO_2Tol$, NH_2 **5**	24	94	71 (*S*)
4	Ph, $NHSO_2CF_3$, Ph, NH_2 **6**	6	67	31 (nd)
5	Ph, $NHSO_2$–3,5-$(CF_3)_2C_6H_3$, Ph, NH_2 **7**	6	82	58 (*S*)
6	Ph, $NHSO_2Tol$, Ph, NH_2 **8**	6	99	71 (*S*)
7	Ph, $NHSO_2$–C_6H_4–OMe, Ph, NH_2 **9**	6	100	73 (*S*)

ee. However, it is important to note that the ligands carrying an aromatic group on the sulfonyl function gave better enantioselectivities.

The second series of reductions were performed with ligands based on diphenylethylene diamine motif **6**–**9** (entries 4–7). The same effect was found as previously described for cyclohexenediamine-based ligands. In order to improve the enantioselectivity, the sulfonyl group needs to be substituted by an aromatic ring. In addition, when the aromatic ring was substituted by electron donating groups, such as MeO, better enantioselectivities were obtained. As all these assays were carried out in the system of formic acid/triethylamine, the best results obtained (entry 7) still gave moderate ee of 73%. This ligand was tried in the system of 2-propanol/KOH and compared with previously obtained results (Table 4).

Table 4. Reduction of **1** with diphenylethylene diamine-based ligands under different reaction conditions

Entry	Reaction medium	T (°C)	Time (h)	GC yield (%)	ee (%) (config)
7	$HCOOH/NEt_3$	20	24	100	73 (*S*)
8	$HCOOH/NEt_3$	20	1	8	73 (*S*)
9	2-Propanol/KOH	20	1	100	75 (*S*)
10	2-Propanol/KOH	1	4	98	82 (*S*)

From the results shown in Table 4, it is clear that the catalytic system is more active with 2-propanol as a hydrogen donor. On the other hand, the enantioselectivity was also enhanced under these conditions. The results demonstrate the possibility of preparing the (*S*)-alcohol with an improved ee of 82% by performing the reaction at a lower temperature, near 0 °C.

3. Conclusion

This study has shown that both enantiomers of a secondary alcohol could be obtained in good yield and high enantiomeric excess by biocatalysis as an alternative method to the existing chemical methods. Two complementary approaches were developed: microbial reduction of prochiral ketones and asymmetric reduction through asymmetric hydrogen transfer. Both methods were applied in the reduction of **1**.

Microbial reduction gives a quantitative transformation and the selectivities are generally very high. However, the enzymes are cofactor dependent and the cofactor needs

to be recycled for the large-scale preparations. Moreover, the bio-reductions are performed at low substrate concentrations as the enzymes are easily inhibited.

On the other hand, the asymmetric reductions can be performed at high substrate concentrations. The yields are excellent and the enantioselectivities of ketone **1** reductions are moderate.

4. Experimental

4.1. Materials and methods

Microorganisms used in screening are available from either ATCC or DMSZ strain banks. *L. kefir* (ATCC 34511 and DMS 20587) was grown as recommended by ATCC in MRS (Man–Rogosa–Sharp) medium supplied by Difco. BTA was purchased from Aldrich. *R*- and *S*-alcohol were purchased from Indofine. Commercial alcohol dehydrogenase and NAD(P)H were obtained from Fluka. All chemicals and solvents were used without any further purification if not stated otherwise.

4.2. Analytical methods

Reactions were followed by GC on a Varian 3400 with FID and Spectraphysics ChromJet integrator using Chirasil-dex CB column (25 m × 0.25 mm, DF = 0.25) under the following conditions: detector temperature 250 °C, injector temperature 220 °C and helium as a gas carrier. Column temperature was programmed in the range 100–160 °C with the heating rate of 2 °C min^{-1}. A calibration curve was realized for the substrate and both enantiomers of alcohol. Retention times (t_r in minutes) were: 2.96 (**1**), 10.34 [(*S*)-alcohol] and 11.19 [(*R*)-alcohol].

4.3. Enzymatic reduction

To the phosphate buffer of pH 7.8 (100 mM, 1.5 ml), *L. kefir* alcohol dehydrogenase (4.4–5 U/ml) and NADPH (an aliquot of 100 mM solution) were added and the suspension incubated for 30 min at 30 °C. The substrate (7.5 mg, 29.3 μmol) was then added, followed by the addition of 2-propanol (quantities as shown in Table 1) and the mixtures were incubated at 30 °C and 1300 rpm. The samples were drawn at regular time intervals and analyzed by GC after a mini extraction with dichloromethane.

4.4. Microbial screening

Microorganisms known to express the oxido-reductase activities (*A. niger*, *S. cerevisiae*, *Saccharomyces montanus*, *Pichia membranaefaciens*, *Candida parapsilosis*, *Candida guilliemondii*, *Hansenula polymorpha*, *Mucor racemosus*, *Geotrichum candidum*, *Sporotrichum exile* and *Rhodococcus rhodochrous*) were inoculated in a sterile Columbia medium and incubated with shaking at 25–37 °C for 24–48 h depending on the microorganism. *L. kefir* was grown in the static culture in MRS medium at 28 °C for 48 h. Cultures were harvested by centrifugation at 5000 rpm for 15 min at 4 °C, washed with the sterile physiological solution and stored frozen at −30 °C. Frozen biomass was suspended in 100 mM phosphate buffer pH 7. Substrate (100 mM **1** in 2-propanol) was added to obtain 5 mM final concentration and the mixtures were incubated at 30 °C for 24 h. The mixtures were centrifuged and the aqueous solutions were extracted with dichloromethane prior to GC analysis.

4.5. Reduction with *L. kefir*

L. kefir cells were suspended in 100 mM phosphate buffer pH 7 at a concentration of 20 mg ml^{-1}. Substrate was added as a stock solution (100 mM **1** in 2-propanol) to obtain 10 mM final concentration. The reaction mixture was incubated at 30 °C and 1300 rpm. The samples (100 μl) were taken at the time intervals given in Table 2 and Figure 2. An equal volume of dichloromethane was added, the mixture was vortexed three times during a period of 1 min and the biomass removed by centrifugation. The organic layer was analyzed by GC and the yield was determined from a calibration curve.

4.6. Synthesis of monosulfonylated diamine derivatives

Monosulfonylated diamine derivatives were prepared according to the literature procedure.[31]

4.7. Asymmetric hydrogen transfer

Details of the asymmetric hydrogen transfer described herein are with the (1*S*,2*S*)-*N*-trifluoromethanesulfonyl-1,2-cyclohexanedi-amine (ligand **3** from entry 1) as the example. The same protocol and the same scale were applied for all ligands.

4.7.1. Hydrogen transfer in formic acid. The following reagents were charged to a 25 ml round-bottom flask equipped with a condenser: $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 0.05 mmol), ligand **3** (entry 1; 25 mg, 0.1 mmol) and 2-propanol (10 ml). The reaction mixture was stirred under argon at 80 °C for 30 min. The solvent was removed under vacuum and an orange solid was obtained.

To a 25 ml round-bottom flask pre-chilled to 0 °C, triethylamine (3 ml, 21.5 mmol), formic acid (2 ml, 53 mmol) and substrate **1** (1.17 ml, 10 mmol) were placed. The reaction mixture was stirred with argon bubbling for 15 min. The solution was then transferred to the flask containing the catalyst via a cannula. The resulting solution was stirred at room temperature under an argon atmosphere. The samples were drawn and analyzed by GC.

4.7.2. Hydrogen transfer in 2-propanol. The following reagents were charged to a 25 ml round-bottom flask equipped with a condenser: $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 0.05 mmol), ligand **3** (entry 1; 25 mg, 0.1 mmol) and 2-propanol (10 ml). The reaction mixture was stirred under argon at 80 °C for 30 min. Then, 2-propanol (90 ml) and ketone **1** (1.17 ml, 10 mmol) were added. The mixture was degassed by bubbling the argon for 15 min, followed by addition of KOH (14 mg). The resulting solution was stirred at room temperature under argon atmosphere. The samples were drawn and analyzed by GC.

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