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# Stereoselective Reduction of 2-Hydroxy Ketones towards *syn*- and *anti*-1,2-Diols

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**Abstract:** Stereoselective reduction of 2-hydroxy ketones should in principle give access to *syn*- and *anti*-1,2-diols. *anti*-1,2-Diols are accessible in a highly selective way using zinc borohydride [$Zn(BH_4)_2$] under chelation control ($dr > 20:1$). Diastereoselective reduction of unprotected or even protected 2-hydroxy ketones towards *syn*-1,2-diols could be achieved only with moderate selectivity of $dr \leq 5:1$. Even when using sterically demanding protecting groups and/or polymer-supported borohydride reagents high selectivity could not be achieved. A new ionic liquid-dependent borohydride reduction method, although highly attractive with respect to reaction engineering, resulted in only moderate to good selectivity. An efficient two-step biocatalytic method for the synthesis of *syn*-1,2-diols is described. The method relies on the whole-cell *Pichia glucozyma*-catalyzed stereoselective reduction of the unprotected (*R*)-2-hydroxy ketones ($dr > 10:1$). The latter are accessible through thiamine diphosphate-dependent enzyme-catalyzed synthesis starting from simple aldehydes. Thus, biocatalytic transformations enable a process which is hardly accessible through present non-enzymatic methods.

**Keywords:** benzaldehyde lyase; benzoin reaction; biocatalysis; borohydrides; ionic liquids

Enantiopure substituted 1,2-diols are valuable intermediates in the synthesis of drugs and natural products.[1] However, they are often obtained as mixtures of *syn*- and *anti*-diastereomers in varying diastereomeric and/or enantiomeric ratios using either transition metal complexes[2] or organocatalysts.[3] The separation of 1,2-diol stereoisomers can be a difficult task, especially when the separation has to be conducted on a large scale. Therefore the highly stereoselective reduction of 1,2-diketones or 2-hydroxy ketones is a valuable alternative to access *syn*- and *anti*-1,2-diols.

Here, three different methods – based on borohydrides, ionic liquids, and biocatalysts – are applied towards the proposed *syn*- and *anti*-stereoselective reduction of 2-hydroxy ketones. We identified a chemoenzymatic synthesis to enantiopure *syn*-1,2-diols which, due to eco-friendly reaction conditions as well as high stereoselectivities, offers a valuable complement to the known *anti*-selective reduction with $Zn(BH_4)_2$.

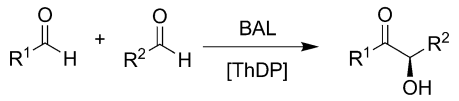
The crucial step is a stereoselective reduction of the corresponding (*R*)-2-hydroxy ketones, which can be easily obtained by benzaldehyde lyase (BAL)-catalyzed cross benzoin reaction of aliphatic/aromatic and aromatic aldehydes on a preparative scale (Table 1).[4]

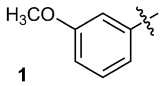
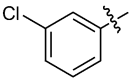
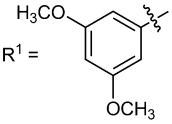
(*R*)-3,3′-Dimethoxybenzoin (**1**) and three different (*R*)-acyloins (**2**–**4**), were prepared in good yields and with high enantioselectivity ($ee \geq 97\%$, Table 1). Compounds **1**–**4** were used as model substrates towards the synthesis of *syn*- and *anti*-1,2-diols. Additionally, *rac*-**1** was prepared by $CN^-$-catalyzed benzoin reaction of 3-methoxybenzaldehyde in 26% yield.

(*R*)-2-Hydroxy ketones **1**–**4** were reduced in a highly diastereoselective manner using known $Zn(BH_4)_2$ reagent,[5] yielding *anti*-1,2-diols with $dr \geq 20:1$ (Table 2). The high diastereoselectivity is gov-

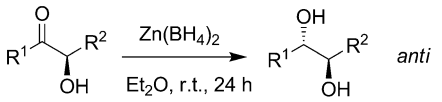
**Table 1.** Stereoselective synthesis of 2-hydroxy carbonyl compounds catalyzed by benzaldehyde lyase (BAL).[a]




| Entry | 2-Hydroxy ketone | Yield [%] | *ee* [%][b] |
|---|---|---|---|
| 1 | $R^1 = R^2 =$  **1** | 96 | >99 |
| 2 | $R^1 =$  $R^2 = CH_3$ **2** | 94 | >99 |
| 3 | $R^1 =$  $R^2 = CH_3$ **3** | 94 | >99 |
| 4 | $R^1 =$  $R^2 = CH_3$ **4** | 95 | 97 |

[a] For reaction conditions and analytical data see ref.[4]
[b] *ee* was determined by chiral phase HPLC.

**Table 2.** *anti*-Selective reduction of 2-hydroxy ketones **1**–**4**.




| Entry | Reactants | Yield [%][a] | *anti*:*syn*[b] |
|---|---|---|---|
| 1 | **1** | 97 | >99:1 |
| 2 | **2** | 33 | 99:1 |
| 3 | **3** | 95 | 97.5:2.5 |
| 4 | **4** | 87 | 98.5:1.5 |

[a] Isolated yield of the mixture of diastereomers.
[b] Ratios were determined by $^1$H NMR spectroscopy.

erned by the stability of the chelated transition state as well as by the bulkiness of $R^2$. The transition state leading to the formation of *anti*- (or synonymous *erythro*-) isomer is much more favoured compared to the transition state leading to the *syn*- (*threo*-) isomer.[6]

Selective access to *syn*-1,2-diols through reduction of 2-hydroxy ketones is more tedious by chemical methods. Ikariya et al. demonstrated highly stereoselective reduction of racemic benzoin to *syn*-hydrobenzoin (*de*>99%) using a ruthenium catalyst, which proceeds through a dynamic kinetic resolution of benzoin.[2a] However, the enediol is formed as an intermediate, which would result in a loss of stereoinformation starting from enantioenriched 2-hydroxy ketones.

In order to obtain *syn*-1,2-diols, protected (*R*)-2-hydroxy ketones were reduced using various metallo hydrides such as aluminium hydrides and several borohydride reducing agents. Compared to the reduction of unprotected 2-hydroxy ketones (Table 2), protected derivatives (**1a**, **1b**, **2a**, **2b**) gave inconsistent results in terms of stereoselectivities (Table 3). A switch in selectivity was also observed, as reduction proceeds *via* an open chain model which can result predominantly in the formation of the *syn*- (*threo*-) isomers.[6] Reduction of *rac*-**1a** (R=TBS) with $Zn(BH_4)_2$ gave the *anti*-isomer (*syn*:*anti* ratio of 30:70, Table 3, entry 1) with only slight preference.

However, *rac*-**1b** (R=MOM) resulted in better selectivities in most cases using the different reducing agents. For example, $Zn(BH_4)_2$ reduces *rac*-**1b** selectively towards the *anti*-product with 78% isolated yield (Table 3, entry 3). Aluminium hydrides such as $LiAlH_4$ as well as DIBAL-H gave good to moderate diastereoselectivities of 18:82 and 10:90 (*syn*:*anti*) towards the same major isomer (Table 3, entries 4 and 5). Compound **2a** (R=TBS) on reduction with $Zn(BH_4)_2$ gave a poor diastereomeric *syn*:*anti* ratio of 55:45 (Table 3, entry 6).

The use of $NaBH_4$ and polymer-supported borohydride resulted in better selectivities of *syn*-1,2-diols with a *syn*:*anti* ratio of 83:17 (Table 3, entries 7 and 8). A change in solvent from methanol to 2-propanol resulted in a slight decrease in selectivity towards the *syn*-1,2-diol (Table 3, entries 8 and 9).

Compound **2b** (R=COPh) on reduction with $Zn(BH_4)_2$ and polymer-supported borohydride, respectively, gave low selectivities towards *syn*- and *anti*-1,2-diols (Table 3, entries 10 and 11).

In summary, the reduction of protected 2-hydroxy ketones gave inconsistent results in terms of diastereoselectivities and thus cannot be used as a general method for the preparation of *syn*-1,2-diols. Highest selectivities of up to 83:17 towards the *syn*-products were obtained by using sterically demanding protecting groups in combination with $NaBH_4$ or polymer-supported borohydride reagents. These results are in agreement with the *syn*-selectivity observed by Ley et al. for the reduction of phenyl-protected 2-hydroxy ketones using polymer-supported borohydride.[7] However, the high diastereoselectivity of >10:1 (*syn*:*anti*) as described by Ley et al. could not be observed with the tested compounds **2a** and **2b**. Moreover, protection and deprotection steps contribute to the lowering of total yields and are time consuming.

In another attempt to obtain higher stereoselectivities, (*R*)-2-hydroxypropiophenones **3** and **3a** were reduced using an ionic liquid ([1-butyl-1-methyl-pyrrolidinium][$BH_4$]) in $CH_2Cl_2$ as a solvent. Unprotected hydroxy ketone **3** on reduction with the ionic liquid

**Table 3.** Reduction of protected 2-hydroxy ketones through metallo hydrides.

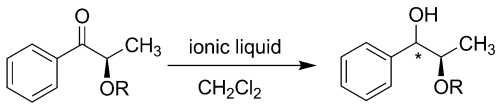

| Entry | Reactants | Reducing agent | Yield [%][b] | *syn*: *anti*[d] |
|---|---|---|---|---|
| 1 | *rac*-**1a** (R = TBS) | $Zn(BH_4)_2$[a] | 95 | 30:70 |
| 2 | *rac*-**1b** (R = MOM) | $NaBH_4$ | 89 | 13:87 |
| 3 | *rac*-**1b** | $Zn(BH_4)_2$ | 78 | 0:100 |
| 4 | *rac*-**1b** | $LiAlH_4$ | 85 | 18:82 |
| 5 | *rac*-**1b** | DIBAL-H | 91 | 10:90 |
| 6 | **2a** (R = TBS) | $Zn(BH_4)_2$ | 35 | 55:45 |
| 7 | **2a** | polymer-supported borohydride | 63 | 83:17 |
| 8 | **2a** | $NaBH_4$ in methanol | –[c] | 83:17 |
| 9 | **2a** | $NaBH_4$ in 2-propanol | –[c] | 78:22 |
| 10 | **2b** (R = COPh) | $Zn(BH_4)_2$ | 34 | 63:37 |
| 11 | **2b** | polymer-supported borohydride | –[c] | 35:65 |

[a] Prepared from $ZnCl_2$ and $NaBH_4$ in THF.
[b] Isolated yield of the mixture of isomers.
[c] No purification was performed.
[d] Ratios were determined by $^1H$ NMR of the crude products.

[BMP][$BH_4$] gives the corresponding 1,2-diol in a *syn*:*anti* ratio of 28:72, which is somewhat better than using $NaBH_4$ as a reducing agent (40:60) (Table 4, entries 1 and 2). A switch in selectivity towards the *syn*-diastereomer was observed when compound **3a** (R = TBS) was reduced with $NaBH_4$ and [BMP][$BH_4$] (Table 4, entries 3 and 4). However, there was hardly any difference in the *syn*:*anti* ratios using ionic liquid and $NaBH_4$ when the protected 2-hydroxy ketones were used for reduction.

The high yield, potential practicable operation, feasible utilization of organic solvents, and in some cases better stereoselectivities makes the ionic liquids approach interesting for further elucidation. However, in summary all tested combinations of reducing agents, including ionic liquids, and protected or unprotected 2-hydroxy ketones as substrates did not result in highly *syn*-selective reductions.

**Table 4.** Reduction with ionic liquid borohydride.




| Entry | Reactant | Reducing agent | Conversion | *syn*:*anti*[b] |
|---|---|---|---|---|
| 1 | **3** (R = H) | $NaBH_4$ | 90 | 40:60 |
| 2 | **3** | ionic liquid[a] | 98 | 28:72 |
| 3 | **3a** (R = TBS) | $NaBH_4$ | 70 | 71:29 |
| 4 | **3a** | ionic liquid[a] | 10 | 75:25 |

[a] Ionic liquid used was [1-butyl-1-methyl-pyrrolidinium][$BH_4$] in $CH_2Cl_2$.
[b] The ratios were determined using $^1H$ NMR of the crude products.

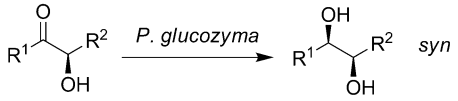
This prompted us to explore the reduction of 2-hydroxy ketones using biocatalysts. The stereoselective reduction of acyloin **3** by alcohol dehydrogenase from a *Thermoanaerobium* species to the *syn*-1,2-diol (*dr* = 99:1) has been demonstrated earlier.[8] However, substituted derivatives such as **2** and **4** were not accepted by this NADPH-dependent enzyme. The use of *Lactobacillus brevis* ADH (LBADH) and alcohol dehydrogenase from *Rhodococcus rubber* and ADH from *Theromoanaerobacter* sp. has been reported recently for the preparation of *syn*- and *anti*-diols.[9]

Several reports have been published for the reduction of benzils to chiral benzoins using conventional biocatalysts such as baker's yeast or whole cells of *Bacillus cereus*.[10] The non-conventional yeast *Pichia glucozyma* has been previously used to carry out the enantioselective reduction of different α-keto aryl groups, including various benzils.[11] The use of this biocatalyst, mainly as a whole cell transformation, offers an attractive alternative due to the mild and eco-friendly reaction conditions as well as *in-situ* regeneration of expensive cofactors. Therefore, whole cells of *P. glucozyma* (CBS 5766) were tested for the reduction of the unprotected (*R*)-2-hydroxy ketones **1**–**4**.

The reactions were performed in potassium phosphate buffer (pH 7). Ethanol (2.5% vol) was added as a cosolvent in order to increase the substrate solubility and also as cosubstrate for cofactor regeneration. The batch reactions were carried out on scales between 0.04 and 0.4 mmol of the respective 2-hydroxy ketone (Table 5).

**Table 5.** Biocatalytic reduction of unprotected (*R*)-2-hydroxy ketones **1**–**4** to *syn*-1,2-diols by *P. glucozyma*.




| Entry | Hydroxy ketones | Yield [%][a] | *syn*:*anti*[b] |
|---|---|---|---|
| 1 | **1** | – | – |
| 2 | **2** | 82 | 95.5:4.5 |
| 3 | **3** | 67 | 97.5:2.5 |
| 4 | **4** | 52 | >98:2 |

[a] Isolated yield of the products.
[b] Ratios were determined by $^1$H NMR.

(*R*)-2-Hydroxy ketones **1**–**4** were reduced to the corresponding *syn*-1,2-diols with good diastereoselectivity ($dr > 10:1$) (Table 5, entries 2–4), with the exception of compound **1** which, probably due to steric reasons, does not undergo reduction through whole cells of *P. glucozyma* (Table 5, entry 1).

*P. glucozyma* promises to become a valuable tool in organic chemistry for the stereoselective reduction of 2-hydroxy ketones like benzoins and phenylpropanone derivatives. Encouraged by these results we will extend our studies on *P. glucozyma* with the aim to overcome the limitations due to steric reasons shown above.

In combination with thiamine diphosphate-dependent enzymes the presented methodology enables a convergent route for the enantioselective synthesis of valuable *syn*- and *anti*-1,2-diols starting from readily available achiral aldehydes. We are working towards the enzymatic access to (*S*)-2-hydroxy ketones, which has partially been solved already.[12] It has to be shown whether the enzyme from *P. glucozyma* or its variants will accept these as substrates as well.

The combination of the two biocatalytic steps shown above will result in a possible one-pot transformation without the requirement of protecting groups to achieve high stereoselectivity towards the synthesis of *syn*-1,2-diols. This nicely complements the widely applicable *anti*-selective reduction of 2-hydroxy ketones using $Zn(BH_4)_2$.

## Experimental Section

### General Procedures for the Reduction of 2-Hydroxy Ketones with Cells from *Pichia glucozyma* CBS 5766

Reductions were carried out in 15-mL screw-capped test-tubes with a reaction volume of 10 mL; 1.8 mL of wet cells (corresponding to 200 mg of dry cells) were suspended in 8.2 mL of 0.1 M phosphate buffer pH 7.0. Substrates were dissolved in ethanol until reaching a concentration of 40 g L$^{-1}$(if the solution is not clear the suspension can be gently heated); 250 μL of this solution were added to the cells suspension. Ethanol acted as a cosolvent and cosubstrate for cofactor regeneration. Reactions were carried out under magnetic stirring at 28 °C. Work-up was performed with EtOAc and products were purified by column chromatography (see Supporting Information).

## Acknowledgements

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