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Biocatalytic Strategies for the Asymmetric Synthesis of α-Hydroxy Ketones

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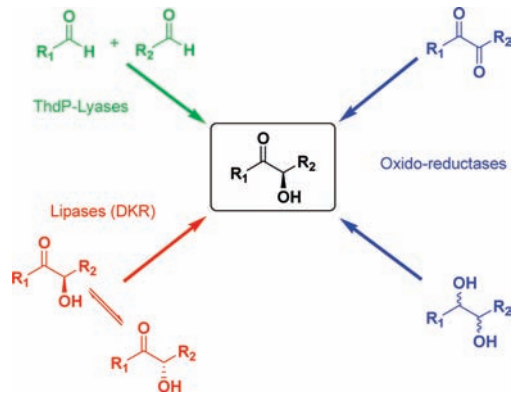
CONSPECTUS

The development of efficient syntheses for enantiomerically enriched α-hydroxy ketones is an important research focus in the pharmaceutical industry. For example, α-hydroxy ketones are found in antidepressants, in selective inhibitors of amyloid-β protein production (used in the treatment of Alzheimer's), in farnesyl transferase inhibitors (Kurasoin A and B), and in antitumor antibiotics (Olivomycin A and Chromomycin A3). Moreover, α-hydroxy ketones are of particular value as fine chemicals because of their utility as building blocks for the production of larger molecules. They can also be used in preparing many other important structures, such as amino alcohols, diols, and so forth. Several purely chemical synthetic approaches have been proposed to afford these compounds, together with some organocatalytic strategies (thiazolium-based carboligations, proline α-hydroxylations, and so forth). However, many of these chemical approaches are not straightforward, lack selectivity, or are economically unattractive because of the large number of chemical steps required (usually combined with low enantioselectivities).



In this Account, we describe three different biocatalytic approaches that have been developed to efficiently produce α-hydroxy ketones:

(i) *The use of thiamine diphosphate-dependent lyases (ThDP-lyases) to catalyze the umpolung carboligation of aldehydes.* Enantiopure α-hydroxy ketones are formed from inexpensive aldehydes with this method. Some lyases with a broad substrate spectrum have been successfully characterized. Furthermore, the use of biphasic media with recombinant whole cells overexpressing lyases leads to productivities of ∼80−100 g/L with high enantiomeric excesses (up to >99%).

(ii) *The use of hydrolases to produce α-hydroxy ketones by means of (in situ) dynamic kinetic resolutions (DKRs).* Lipases are able to successfully resolve racemates, and many outstanding examples have been reported. However, this approach leads to a maximum theoretical yield of 50%. As a means of overcoming this problem, these traditional lipase-catalyzed kinetic resolutions are combined with racemization of remnant substrate, which can be done in situ or in separate compartments. Examples showing high conversions (>90%) and enantiomeric excesses (>99%) are described.

(iii) *Whole-cell redox processes, catalyzed by several microorganisms, either by means of free enzymes (applying a cofactor regeneration system) or by whole cells.* Through the use of redox machineries, different strategies can lead to high yields and enantiomeric excesses. Some enantiopure α-hydroxy ketones can be formed by reductions of diketones and by selective oxidations of vicinal diols. Likewise, some redox processes involving sugar chemistry (involving α-hydroxy ketones) have been developed on the industrial scale. Finally, the redox whole-cell concept allows racemizations (and deracemizations) as well.

These three strategies provide a useful and environmentally friendly synthetic toolbox. Likewise, the field represents an illustrative example of how biocatalysis can assist practical synthetic processes, and how problems derived from the integration of natural tools in synthetic pathways can be efficiently tackled to afford high yields and enantioselectivities.

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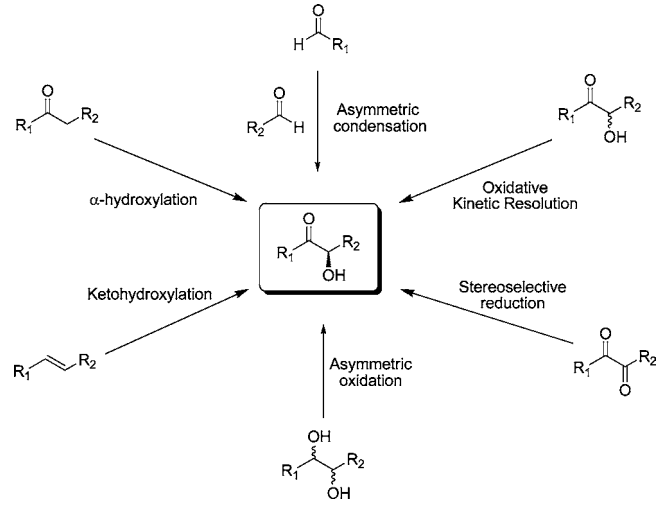
1. Introduction

From a chemical viewpoint, α-hydroxy ketones (also called acyloins) are highly valuable building blocks for many applications for the fine chemistry sector as well as pharmaceuticals. For instance, α-hydroxy ketones are found in some antidepressants, in selective inhibitors of amyloid-β protein production (for Alzheimer's disease treatment), in farnesyl transferase inhibitors Kurasoin A and B, in antifungal agents, or in some antitumor antibiotics (Olivomycin A, Chromomycin A_3, and epothilones). In addition, they can be used for the further formation of many other important structures (e.g., amino alcohols, diols, etc.) (Figure 1).[1,2]

In virtue of the importance of α-hydroxy ketones, several chemical approaches aiming to prepare them have been reported.[3] Probably the most employed strategies are the α-hydroxylation of ketones through the enantioselective enolate oxidation (formed in situ, catalyzed by chiral oxidants), and the Sharpless asymmetric dihydroxylation of the silylenol ether of the corresponding ketone.[4] Other chemical approaches are the ketohydroxylation of olefins,[5] the asymmetric mono-oxidation of the correspondent 1,2-diols,[6] as well as the oxidative kinetic resolution of racemic α-hydroxy ketones.[7] Furthermore, some organocatalytic strategies have been proposed. These involve the direct asymmetric α-oxygenation of ketones in the presence of, for example, proline or alanine[8] as well as the traditional benzoin condensation, carried out stereoselectively by means of optically active catalysts such as chiral thiazolium and triazolium salts, in a biomimetic fashion[9] (Scheme 1).

SCHEME 1. Overview of the Chemical Strategies for the Synthesis of Asymmetric α-Hydroxy Ketones[3−9]



As depicted, there are many chemical possibilities for the synthesis of asymmetric α-hydroxy ketones (Scheme 1). Yet, although there are some successful examples of molecules

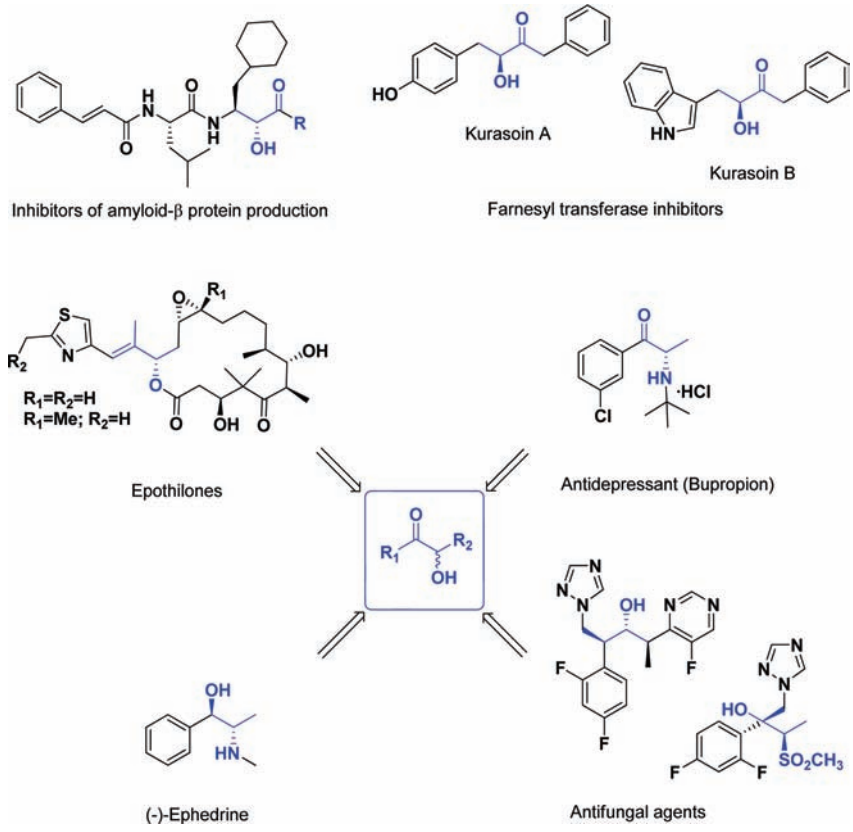
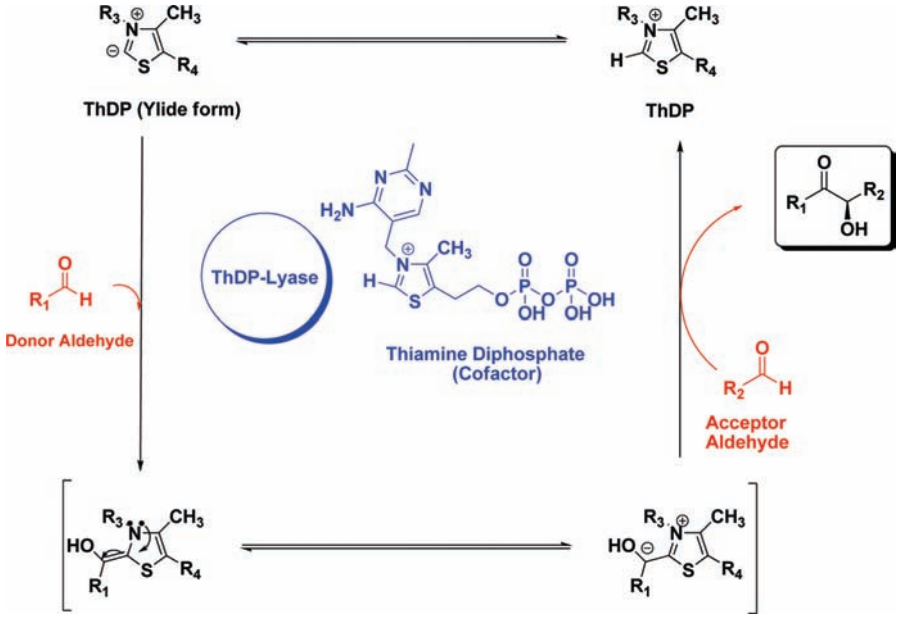


FIGURE 1. Examples of compounds bearing α-hydroxy ketones as well as some products derivatized thereof.[1,2]

SCHEME 2. Proposed Mechanism for the ThDP-Lyase-Catalyzed *Umpolung* Carboligation of Aldehydes[13]



produced through these strategies, in many cases, syntheses demand a significant number of chemical steps, thus lowering overall yields and increasing the waste production. Furthermore, high enantioselectivities are rather rare.

To overcome these challenges, biocatalysis encompasses many strategies to afford a wide number of important chemical structures, which can be obtained with high enantio-, regio-, and chemoselectivities. Moreover, in many cases, these selectivities can be combined with economic and environmentally friendly synthetic conditions.[10,11] Given the synthetic importance of α-hydroxy ketones, several enzymatic concepts to efficiently produce these chemicals have been developed, starting from proof-of-principles and leading in some cases to mature processes (even at the commercial level). Overall, the topic is illustrative on how biocatalysis can be applied in many diverse, multidisciplinary ways, by combining biology, organic synthesis, and process development. Herein, we want to report on recent, relevant developments in this particular area.

2. Thiamine-Diphosphate-Dependent (ThDP) Lyases: Biocatalysts for the *Umpolung* Carboligation of Aldehydes

Thiamine-diphosphate-dependent lyases (ThDP-lyases) catalyze the *umpolung* carboligation of aldehydes to afford chiral α-hydroxy ketones. Several ThDP-lyases have been characterized as powerful biocatalysts, such as pyruvate decarboxylase (PDC), benzoylformate decarboxylase (BFD), and benzaldehyde lyase (BAL).[12] Key in the catalysis is the reaction of the cofactor (thiamine diphosphate) with the "donor" aldehyde, to form an active enamine carbanion. Subsequently, the "acceptor" aldehyde attacks the carbanion to form the α-hydroxy ketone (Scheme 2). Interestingly, in many cases, donor and acceptor aldehydes can be different, thus allowing the production of many useful building blocks. The mechanism, together with the interaction between the cofactor and lyases, has been extensively studied, either by considering chemical reactivities of both aldehydes and thiamine or by means of molecular biology strategies (i.e., directed evolution).[13]

To convert a biocatalytic *academic curiosity* into a (powerful) practical application, obviously the use of the biocatalyst (either as enzyme or as whole cell) must clearly bring an (economic) added value. In this respect, the identification of lyases able to accept a broad substrate range is obviously an asset. As a relevant example, benzaldehyde lyase (BAL) from *Pseudomonas fluorescens* catalyzes the carboligation of both aromatic and aliphatic aldehydes, thus forming many enantiopure (*R*)-α-hydroxy ketones[12,14] (Figure 2). As depicted (Figure 2), BAL is able to accept an ample number of aldehydes as substrates. This capability affords the performance of *cross* carboligations between different aldehydes (e.g., benzaldehyde and acetaldehyde). This option opens new possibilities in processes catalyzed by BAL. Yet, in some of these cases, also BAL-catalyzed self-condensations of aldehydes (e.g., acetoin synthesis) are observed as the byproduct. A proper substrate addition is therefore key for reaching selective processes.

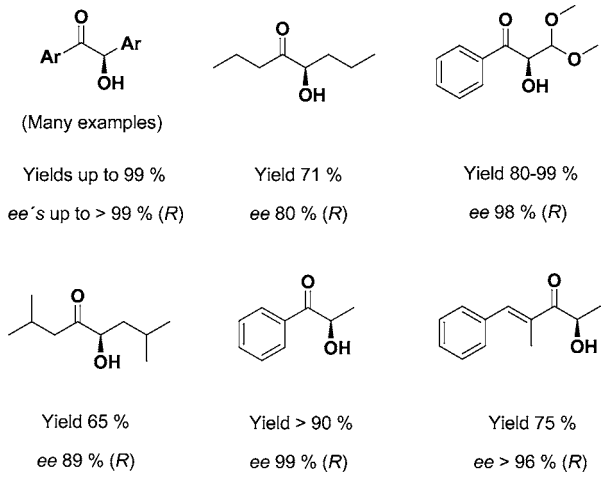


FIGURE 2. Selected examples of chiral α-hydroxy ketones produced by means of BAL as biocatalyst, starting from aldehydes.[12,14]

Several lyase-catalyzed processes have been set up and even implemented at the industrial scale. For instance, the use of pyruvate decarboxylases (PDC) for the production of *L*-phenylacetylcarbinol (PAC) from benzaldehyde and pyruvic acid is actually one of the first biocatalyzed whole-cell processes ever reported and implemented at the production scale (to further produce ephedrine).[12c] This process was developed almost a century ago, by using PDC contained in whole cells from *Saccharomyces cerivisiae*, with PAC productivities of ca. 10−15 g/L.[15] During the following decades, further improvements (productivities of >100 g/L) based on the same process concept were introduced, such as new set ups and new microorganisms (e.g., *Candida utilis* or *Zymomonas mobilis*). Likewise, the use of nonconventional media, such as supercritical CO_2, was recently described. This latter approach may be a relevant concept, since less waste production is expected (though the strategy is energetically demanding), together with no need for an organic solvent for the downstream processing. Until now, overall yields of ca. 20 g/L for *L*-PAC and ca. 50 g/L for (−)-ephedrine have been disclosed (Scheme 3).[16]

Likewise, many biocatalytic practical concepts have been developed by using BAL as biocatalyst, such as, for example, biphasic systems,[17] continuous processes,[18] gas reactors,[19] and enzyme immobilization.[20] Moreover, the direct use of *E.coli* whole cells overexpressing BAL as biocatalysts in a biphasic system has been reported.[21] This whole-cell approach is promising, since besides advantages derived from the use of a biphasic system (in terms of high substrate concentrations) the external addition of (expensive) organic cofactor (ThDP) can be avoided, thus decreasing process costs significantly. Many different chiral α-hydroxy ketones can be produced with high productivities and enantioselectivities (Scheme 4).[21]

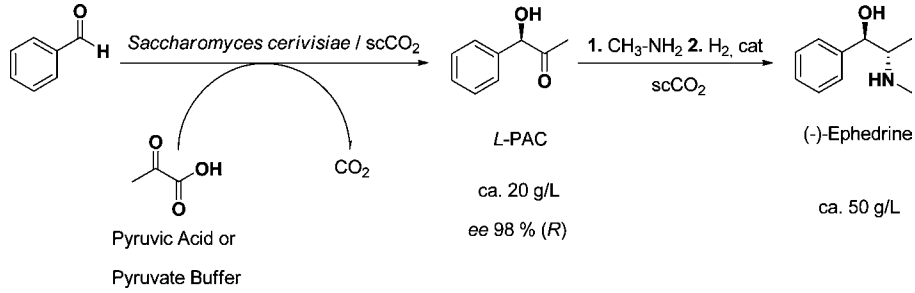
3. Hydrolase-Catalyzed (in Situ) Dynamic Kinetic Resolutions (DKRs)

The hydrolase-catalyzed (lipases and esterases) kinetic resolution (KR) of racemates has proven to be an efficient method to afford enantiopure compounds.[10,22] Several KR processes to synthesize chiral α-hydroxy ketones have been described as well, using different lipases and esterases as biocatalysts.[23] A wide number of structurally different α-hydroxy ketones have been produced, involving cyclic and aliphatic compounds,[24,25] alkyl-aryl α-hydroxy ketones,[26] or diaryl α-hydroxy ketones.[27] As a relevant example, the production of chiral alkyl-aryl α-hydroxy ketones has been obtained through two strategies: Demir et al. carried out the fungus-catalyzed kinetic resolution of the acetates,[26d] whereas Jeon et al. reported the enantioselective transesterification of the racemic α-hydroxy ketones catalyzed by immobilized lipase B from *Candida antarctica* (CALB) in organic solvents (Scheme 5).[26e]

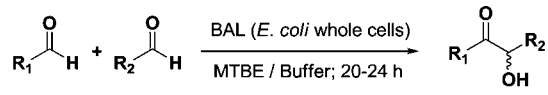
Likewise, lipase-catalyzed kinetic resolutions to afford building blocks for the synthesis of pharmacologically interesting epothilones (see Figure 1) have been disclosed. Thus, in aqueous conditions, different esters of linear α-hydroxy ketones can be enantioselectively hydrolyzed, leading to high yields and enantiomeric excesses, by means of lipase B from *Candida antarctica* (CALB) and lipase from *Burkholderia cepacia* (BCL) (Scheme 6).[25c,d] However, KR processes can only reach a maximum theoretical yield of 50%. To overcome this problem, dynamic kinetic resolutions (DKRs) have been put forward. Thus, a (in situ) racemization of the remnant substrate under KR conditions would theoretically lead to a 100% yield (Scheme 7). In some (few) cases, the in situ base-mediated racemization of the substrate can be applied, as reported by Taniguchi and Ogasawara for the resolution of different tricyclic acyloins, by using a *Burkholderia cepacia* lipase.[29] In other cases, efficient two-compartment DKR processes have been developed,[30] involving *Candida antarctica* lipase B (CALB) as biocatalyst for the enantioselective substrate transesterification in a first compartment, and the simultaneous racemization of the remnant alcohol mediated by Amberlyst 15 in a spatial-separated compartment (Scheme 8).

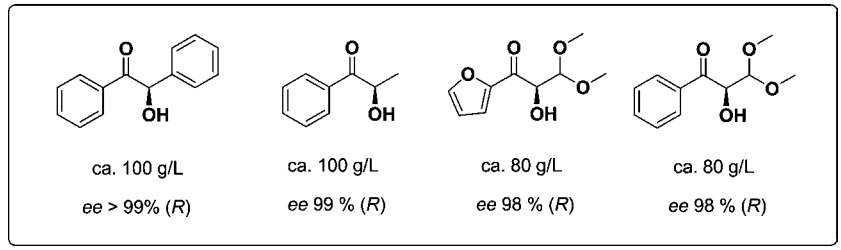
One of the most widely applied strategies is the combination of an enzymatic KR with an in situ transition-metal-catalyzed substrate racemization, via hydrogen transfer, by means of several ruthenium complexes (e.g., Shvo catalyst, Scheme

SCHEME 3. Biocatalytic Process Catalyzed by PDC in Supercritical CO_2, Recently Disclosed[16]

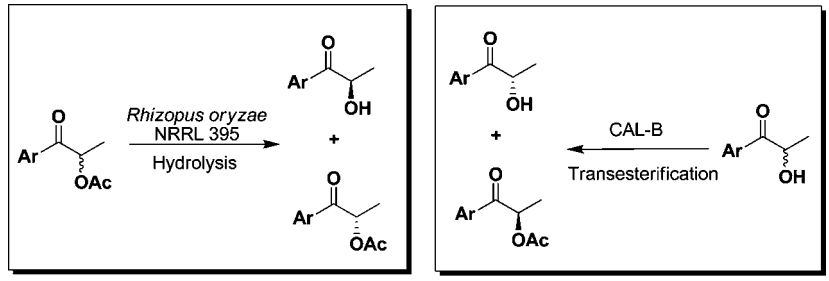


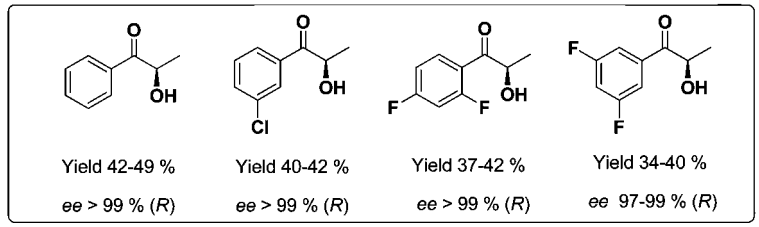
SCHEME 4. Reaction Setup for BAL-Catalyzed Biphasic System Using *E. coli* Whole Cells (Overexpressing BAL); Examples of Molecules and Productivities[21]





SCHEME 5. Two Approaches for the Hydrolase-Catalyzed Kinetic Resolution of Alkyl-Aryl α-Hydroxy Ketones[26d,e]

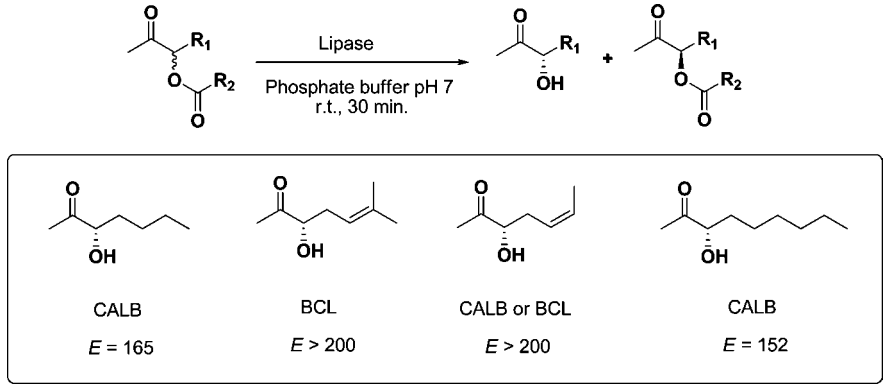




9).[31] Yet, due to the intrinsic racemization mechanism via hydrogen transfer (Scheme 9), when the substrate is a "nonsymmetric" α-hydroxy ketone (R_1 and R_2 are different groups), the DKR fails, since an intermediate diketone would be formed, subsequently leading to the formation of different regioisomers (Scheme 10). To overcome this problem, Bógar et al. described another strategy based on an efficient DKR of allylic alcohols,[31] using CALB for the enantioselective resolution and a ruthenium-complex-mediated racemization of the substrate. Subsequently, the enantiopure acylated-allylic alcohols formed in the DKR were oxidized, affording the desired optically active nonsymmetric acyloins with very high conversions and enantiopurities (Scheme 11).[31]

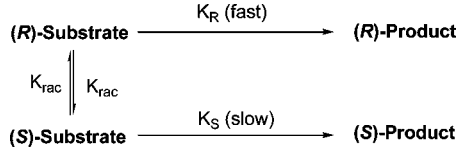
Conversely, when "symmetric" benzoins (1,2-diaryl-2-hydroxyethanones) are used as substrates ($R_1 = R_2$), efficient DKRs can be set, by combining *Pseudomonas stutzeri* lipase-catalyzed enantioselective acylation of the substrate with an in situ racemization of the remnant alcohol, catalyzed by

SCHEME 6. Lipase-Catalyzed Kinetic Resolution of A-Hydroxy Ketones Useful As Precursors for the Synthesis of Epothilones[a]

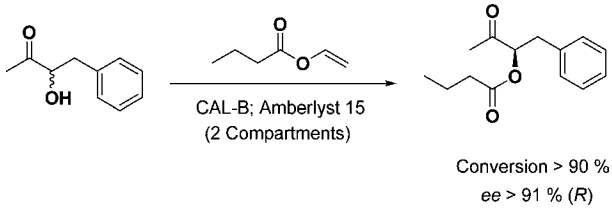


[a] In all cases, yields of >40% were obtained.[25c,d]

SCHEME 7. DKR Process: Enzyme Catalyzes the Conversion of Substrates to Products ($K_R \gg K_S$), whereas Another Catalyst Racemizes the Remnant Substrate[28]



SCHEME 8. Example of Two Compartment DKR of Racemic Acyloins[30]



Shvo's catalyst (Scheme 6).[32] High conversions and excellent enantioselectivities were obtained in a broad range of different (symmetric) benzoins. However, due to the enzyme thermal deactivation at 50 °C (required temperature for the racemization step), the process had to be conducted in three different steps, with some additions of fresh lipase. Proper immobilization of *Pseudomonas stutzeri* lipase in silicone spheres enhanced its activity and stability at high temperature.[33] This led to the development of a highly efficient one-pot DKR of several benzoins at 60 °C. Moreover, lipase immobilization allowed its recovery and reuse, thus promoting a significant enhancement of the productivity of the DKR process (Scheme 12).[32,33]

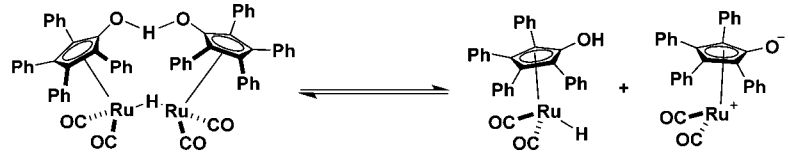
4. Oxido-Reductases for the Asymmetric Synthesis of α-Hydroxy Ketones

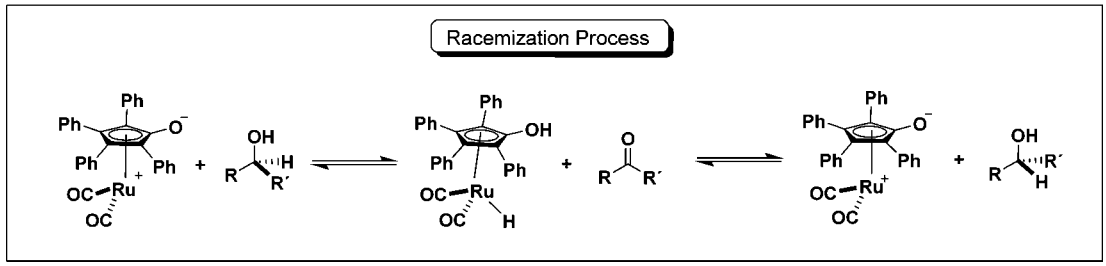
The field of oxido-reductases represents an important example of a mature technology, from which many relevant building blocks can be efficiently produced by performing reductions, oxidations, as well as (de)racemization processes.[34] To afford enantioenriched α-hydroxy ketones by means of oxido-reductases, three general strategies have been put forward: reduction of α-diketones catalyzed by dehydrogenases (DH), oxidation of *vic*-diols by dehydrogenases and oxidases (Ox), and (de)racemization of racemic α-hydroxy ketones (Scheme 13).

These enzymatic reactions can be catalyzed either by isolated enzymes or by whole cells having cell-bound enzymes accessible for the substrates.[34] Oxido-reductases are cofactor-dependent (mostly NAD(P)H/NAD(P)$^+$), and one major challenge is therefore to supply an efficient method for regeneration of the consumed cofactor. In this regard, effective biocatalyzed redox processes can be achieved using whole cells, which provide cofactor regeneration by adding "suicide" cosubstrates (e.g., glucose, formic acid, ethanol, glycerol), which can be oxidized by other dehydrogenases occurring in the cell. The use of wild-type whole cells is often hampered by side reactions and/or low volumetric yields. Alternatively, enzymatic redox processes can be carried out using isolated enzymes which ensure high enantioselectivities, yet this approach demands an adequate system for cofactor regeneration. To complement and, in many cases, overcome these issues, the successful cloning and overexpression of several redox enzymes has led to the "designer bug" concept, with outstanding processes with high yields and enantioselectivities (>200 g L^{-1} d^{-1}, ee's up to >99%).[35]

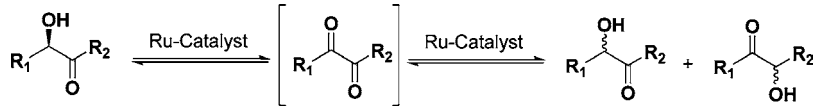
Stereoselective bioreductions of α-diketones have been accomplished by means of different microorganisms as whole-cell biocatalysts, for example, for the reduction of aliphatic α-diketones with different microorganisms.[36] Also, a considerable amount of research pursued the formation of both the enantiomers of different asymmetric benzoins by reduction of the corresponding α-diketones (Scheme 14).[37] In some cases,

SCHEME 9. Ruthenium Complex (Shvo Catalyst) and Racemization Mechanism[31]

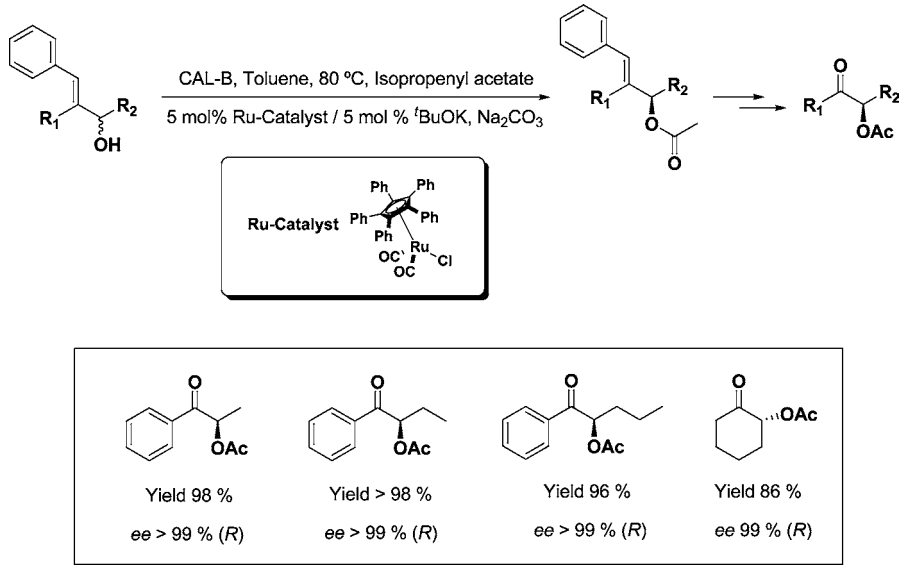




SCHEME 10. Racemization of "Nonsymmetric" α-Hydroxy Ketones ($R_1 \neq R_2$), in Which Different New Substrates Are Formed



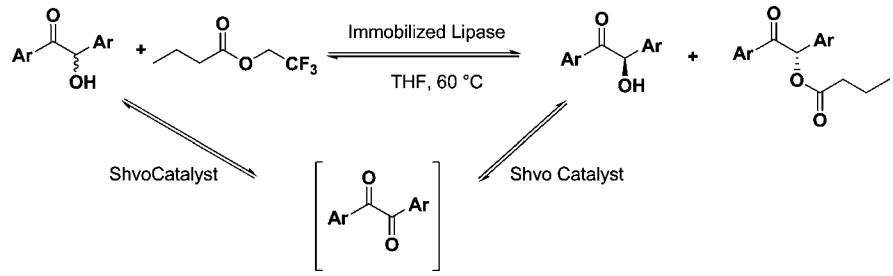
SCHEME 11. Chemoenzymatic DKR of Allylic Alcohols, for the Subsequent Formation of Enantiopure Acyloins[31]



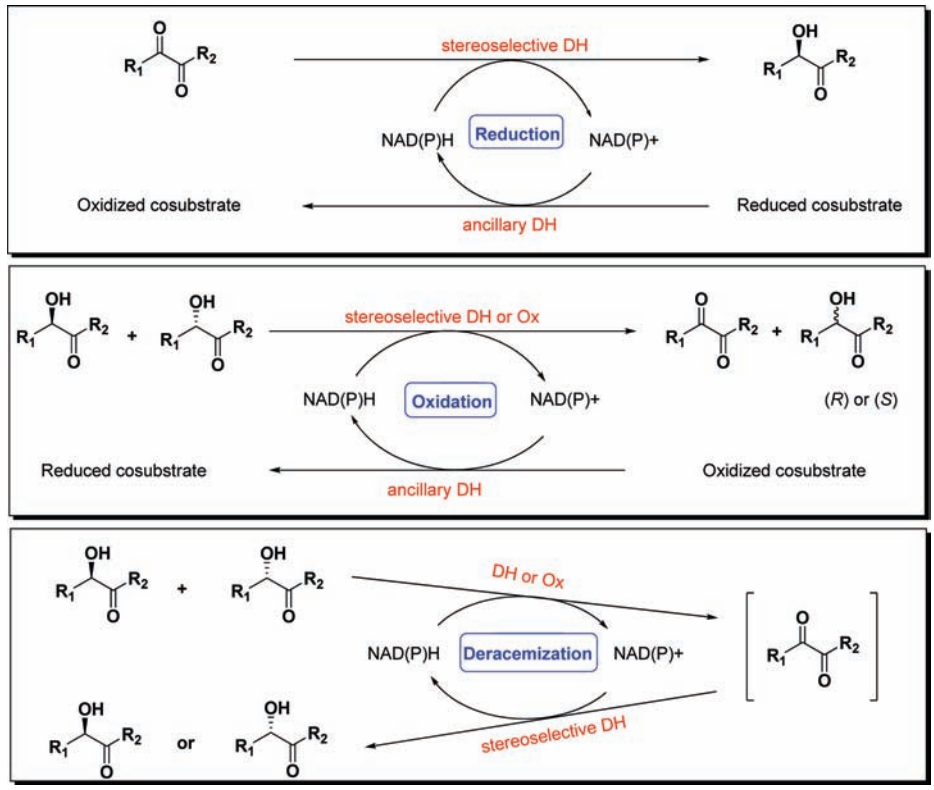
a full reduction to diols was observed as well, presumably because the whole cell contains other competing ketoreductases. Conversions and enantioselectivities have thus been improved by applying enzyme inhibitors, thermal deactivations, use of organic cosolvents, and so on.[38] Further cloning and overexpression of the desired enzymes would certainly lead to proper practical biocatalysts,[35] provided that, if needed, native ketoreductases of the heterologous host were eventually knocked out.[39] These reported methods, despite the success for other bioreductions, have not been so far sufficiently exploited for the efficient preparation of α-hydroxy ketones.

Apart from the above-described reductions, selective bioxidations of *vic*-diols catalyzed by dehydrogenases and/or oxidases may be exploited to obtain enantiopure α-hydroxy ketones. For instance, whole cells of *Bacilus stearothermophilus* are able to enantiospecifically oxidize different aliphatic *vic*-diols to afford α-hydroxy ketones, albeit with low conver-

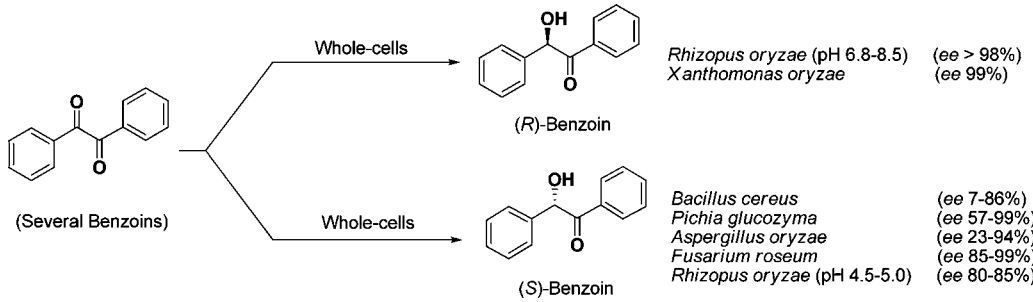
SCHEME 12. One-Pot DKR of "Symmetric" Benzoins (1,2-Diaryl-2-hydroxyketones, Ar=Ar), by Using Immobilized *Pseudomonas stutzeri* Lipase and Shvo Catalyst[32,33]



SCHEME 13. Overview of Three Biocatalytic Approaches for the Synthesis of Enantioenriched α-Hydroxy Ketones[34]



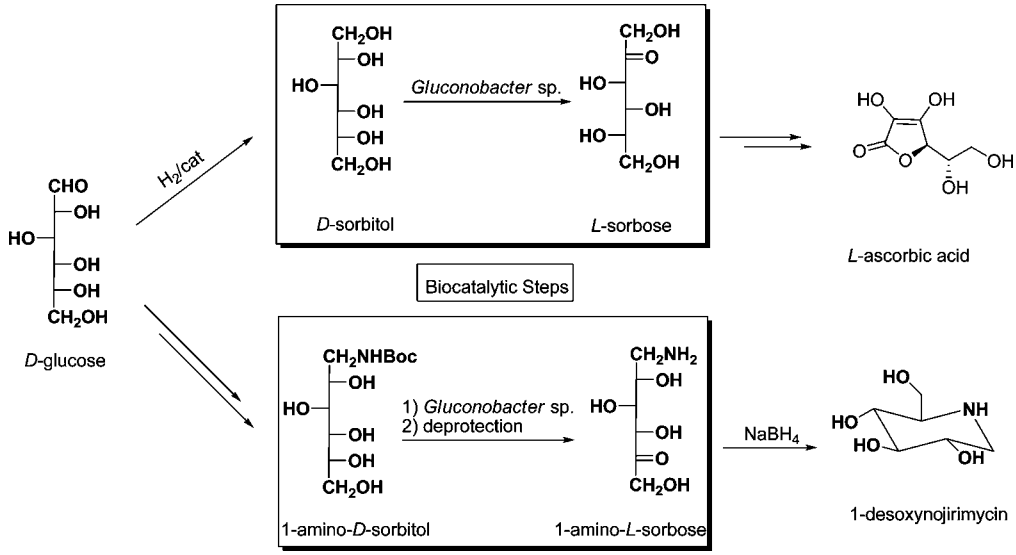
SCHEME 14. Stereoselective Reduction of 1,2-Diaryl-Ethanediones to the Corresponding Benzoins Using Whole Microbial Cells[37]



sions (ee's > 99% (*S*), conversions < 20%).[40] Herein, the cloning and overexpression of these biocatalysts might lead to highly efficient synthetic processes.

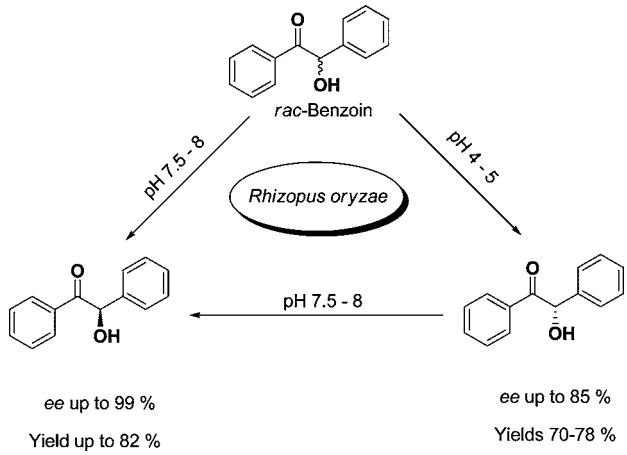
Likewise, oxidation of *vic*-diols is widespread in nature, mainly in enzymatic dehydrogenations of monosaccharides. Different bacteria, especially acetic acid bacteria, and fungi have been used for the selective dehydrogenation of alditols.[41] The most important industrial applications are the oxidation of sorbitol to *L*-sorbose in the Reichstein–Grüssner process for the production *L*-ascorbic acid (vitamin C) and the analogous transformation of

SCHEME 15. Chemoenzymatic Synthesis of Ascorbic Acid and 1-Desoxynojirinycin[a]



[a] The biocatalytic steps are the regio- and stereoselective oxidation of *vic*-diols into α-hydroxyketones.[41]

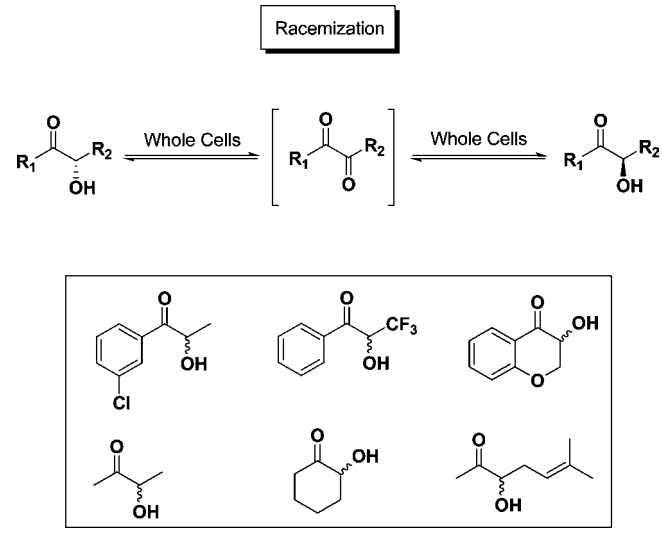
SCHEME 16. Benzoin Deracemization Based on pH Shifts, Catalyzed by *Rhizopus oryzae* Whole Cells[45]



1-amino-*N*-Boc-sorbitol into 1-amino-*N*-Boc-sorbose in the chemoenzymatic synthesis of 1-desoxynojirinycin (Scheme 15). All these biotransformations are catalyzed by *Gluconobacter oxidans* strains.[42] Moreover, other polyalcohols can be regio- and stereoselectively oxidized by bacterial dehydrogenases into α-hydroxy ketones, such as D-arabitol into D-xylulose or *meso*-erythritol into L-erythrulose.[41] Likewise, the dehydrogenation of 2,3-butanediol was tested with different acetic acid bacteria, displaying different outcomes depending on the stereochemistry of the substrate.[43]

Finally, (de)racemizations have also proven to be promising approaches.[34b,44] For instance, the mold *Rhizopus oryzae* is able to catalyze the chirality inversion of benzoins to afford both enantiomers depending on the pH of the medium (Scheme 16, see also Scheme 14).[45] This production of both enantiomers using different reaction conditions suggests the occurrence of different ketoreductases, displaying the highest activity under different pH conditions. Furthermore, other authors have reported racemization technologies by means of lyophilized whole cells of several microorganisms as biocatalysts. Interestingly, the approach was useful for many structurally diverse α-hydroxy ketones (Scheme 17).[46]

SCHEME 17. Whole-Cell-Based Racemization of Chiral α-Hydroxy Ketones[a]



[a] Full racemizations were often obtained in 24−72 h.[46]

5. Concluding Remarks

An overview of several biocatalytic approaches for the efficient production of enantioenriched α-hydroxy ketones has been provided. Overall, the strategies reported by different groups show a mature, multidisciplinary field, in which

many natural tools can be used for practical applications, leading to outstanding enantioselectivities and productivities. This is certainly important for the synthesis of chiral α-hydroxy ketones, as such, very relevant building blocks, but also for applications of biocatalysis in the area of organic synthesis. The processes herein reported may serve as examples for new biocatalytic concepts, as the need for greener, environmentally friendly reactions is presently an important asset in chemical industries. We hope that our contribution can prompt other research groups and industries to undertake research in these areas and to develop novel, efficient, biocatalytic practical processes.

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Francesco Molinari was born in 1961 in Milano, Italy. He received a B.S. in chemistry (1986) under the supervision of Prof. Francesco Sannicolò and Ph.D. (1991) under the supervision of Prof. Cesare Gennari. During these years, his fields of interest were organic synthesis applied to problems of molecular recognition, bifunctional catalysis, and stereoselective carbon−carbon formation. He was a postdoctoral fellow at the Instituto Tecnico of Lisbon working on extractive bioconversions with Prof. Joaquim Cabral. He began his independent career at the Industrial Microbiology Section of the Department of Food Science and Microbiology, University of Milano in 1992. Since 2000, he has been Professor of Chemistry and Biotechnology of Fermentations at the University of Milano. Prof. Molinari's research interests include (stereo)-selective biotransformations, production and isolation of microbial secondary metabolites, and wine fermentations. He has been member of the Scientific Board of the Italian Society of General Microbiology and Microbial Biotechnology (SIMGBM) and of the Italian Association of Biocatalysis and Bioseparations (AIBB).

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Pablo Domínguez de María was born in Gran Canaria (Spain) in 1974. He received a B.S. in Pharmacy (1997) and a B.S. in Chemistry (2001), and completed his Ph.D. in 2002 in the Faculty of Pharmacy at Complutense University (Madrid). After 2 years at Degussa AG (Germany) as a postdoctoral research scientist (2003−2004), he moved to AkzoNobel BV (The Netherlands) in 2005. Since July 2009, he has worked as Group Leader in the Institute of Technical and Macromolecular Chemistry, RWTH Aachen University (Germany), within the group of Prof. Dr. Walter Leitner. His main scientific interests are (industrially feasible) biocatalytic processes, new trends in white biotechnology, and biomimetic organocatalytic concepts. In 2005, he was awarded the Young Scientist Prize by the Iberoamerican Academy of Pharmacy.

FOOTNOTES

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REFERENCES

1 (a) Tanaka, T.; Kawase, M.; Tani, S. α-Hydroxy ketones as inhibitors of urease. *Bioorg. Med. Chem.* **2004**, *12*, 501–505. (b) Wallace, O. B.; Smith, D. W.; Deshpande, M. S.; Polson, C.; Felsenstein, K. M. Inhibitors of Aβ production: solid-phase synthesis and SAR of α-hydroxycarbonyl derivatives. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1203–1206. (c) Fang, Q. K.; Han, Z.; Grover, P.; Kessler, D.; Senanayake, C. H.; Wald, S. A. Rapid access to enantiopure bupropion and its major metabolite by stereospecific nucleophilic substitution on an α-ketotriflate. *Tetrahedron: Asymmetry* **2000**, *11*, 3659–3663.

2 (a) Adam, W.; Lazarus, M.; Saha-Möller, C. R.; Schreier, P. Biocatalytic synthesis of optically active α-oxyfunctionalized carbonyl compounds. *Acc. Chem. Res.* **1999**, *32*, 837–845. (b) Davis, F. A.; Chen, B. C. Asymmetric hydroxylation of enolates with *N*-sulfonyloxaziridines. *Chem. Rev.* **1992**, *92*, 919–934.

3 (a) Plietker, B. New oxidative pathways for the synthesis of α-hydroxy ketones - the α-hydroxylation and ketohydroxylation. *Tetrahedron: Asymmetry* **2005**, *16*, 3453–3459. (b) Davis, F. A.; Chen, B. C. Formation of C-O bonds by oxygenation of enolates. In *Steroselective synthesis*; Helmchen, G., Hoffman, R. W. , Mulzer, E., Schaumann, E., Eds.; Thieme: Stuttgart-New York, 1996; Vol. 8, pp 4497−4518.

4 Zhou, P.; Chen, B. A.; Davis, F. A. In *Asymmetric oxidation reactions*; Katsuki, T., Ed.; Oxford University Press: Oxford, 2001; pp 128−145.

5 Plietker, B. The RuO_4-catalyzed ketohydroxylation, Part II: A regio-, chemo- and stereoselectivity study. *Eur. J. Org. Chem.* **2005**, *9*, 1919–1929.

6 Onomura, O.; Arimoto, H.; Matsumura, Y.; Demizu, Y. Asymmetric oxidation of 1,2-diols using *N*-bromosuccinimide in the presence of chiral copper catalyst. *Tetrahedron Lett.* **2007**, *48*, 8668–8672.

7 (a) Muthupandi, P.; Alamsetti, S. K.; Sekar, G. Chiral iron complex catalyzed enantioselective oxidation of racemic benzoins. *Chem. Commun.* **2009**, 3288–3290. (b) Alamsetti, S. K.; Muthupandi, P.; Sekar, G. Chiral cobalt-catalyzed enantiomer-differentiating oxidation of racemic benzoins by using molecular oxygen as stoichiometric oxidant. *Chem.—Eur. J.* **2009**, *15*, 5424–5427.

8 (a) Bogevig, A.; Sundén, H.; Córdova, A. Direct catalytic enantioselective α-aminoxylation of ketones: a stereoselective synthesis of α-hydroxy and α,α′-dihydroxyketones. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109–1112. (b) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. Direct proline catalyzed asymmetric α-aminoxylation of ketones. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112–1115.

9 (a) Enders, D.; Kallfass, U. An efficient nucleophilic carbene catalyst for the asymmetric benzoin condensation. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743–1745. (b) Martí, J.; Castells, J.; López-Calahorra, F. Introduction to a rational design of chiral thiazolium salts. *Tetrahedron Lett.* **1993**, *34*, 521–524.

10 (a) Liese, A.; Seebach, K.; Wandrey, C. *Industrial Biotransformations*; Wiley-VCH: Weinheim, 2006. (b) Faber, K. *Biotransformations in Organic Chemistry*; Springer: Verlag, 2004.

11 (a) Patel, R. N. Synthesis of chiral pharmaceutical intermediates by biocatalysis. *Coord. Chem. Rev.* **2008**, *252*, 659–701. (b) Gotor, V.; Alfonso, I.; Garcia-Urdiales, E. *Asymmetric organic synthesis with enzymes*; VCH: Weinheim, 2008.

12 (a) Müller, M.; Gocke, D.; Pohl, M. Thiamine diphosphate in biological chemistry: exploitation of diverse thiamine diphosphate dependent enzymes for asymmetric chemoenzymatic synthesis. *FEBS J.* **2009**, *276*, 2894–2904. (b) Demir, A. S.; Ayhan, P.; Betül Sopaci, S. Thiamine pyrophosphate dependent enzyme catalyzed reactions: Stereoselective C-C bond formations in water. *Clean: Soil, Air, Water.* **2007**, *35*, 406–412. (c) Pohl, M.; Sprenger, G. A.; Müller, M. A new perspective on thiamine catalysis. *Curr. Opin. Biotechnol.* **2004**, *15*, 335–342. (d) Pohl, M.; Lingen, B.; Müller, M. Thiamin-diphosphate dependent enzymes: new aspects of asymmetric C-C bond formation. *Chem.—Eur. J.* **2002**, *8*, 5288–529.

13 (a) Gocke, D.; Walter, L.; Gauchenova, E.; Kolter, G.; Knoll, M.; Berthold, C. L.; Schneider, G.; Pleiss, J.; Müller, M.; Pohl, M. Rational protein design of ThDP-dependent enzymes: engineering stereoselectivity. *ChemBioChem* **2008**, *9*, 406–412. (b) Knoll, M.; Müller, M.; Pleiss, J.; Pohl, M. Factors mediating activity, selectivity and substrate specificity for the thiamin diphosphate-dependent enzymes benzaldehyde lyase and benzoylformate decarboxylase. *ChemBioChem* **2006**, *7*, 1928–1934. (c) Jordan, F. Current mechanistic understanding of thiamin diphosphate-dependent enzymatic reactions. *Nat. Prod. Rep.* **2003**, *20*, 184–201.

14 (a) Cosp, A.; Dresen, C.; Pohl, M.; Walter, L.; Röhr, C.; Müller, M. α,β-unsaturated aldehydes as substrates for asymmetric C−C bond forming reactions with thiamine diphosphate (ThDP)-dependent enzymes. *Adv. Synth. Catal.* **2008**, *350*, 759–771. (b) Domínguez de María, P.; Pohl, M.; Gocke, D.; Gröger, H.; Trauthwein, H.; Stillger, T.; Walter, L.; Müller, M. Asymmetric synthesis of aliphatic 2-hydroxy ketones by enzymatic carboligation of aldehydes. *Eur. J. Org. Chem.* **2007**, 2940–2944. (c) Demir, A. S.; Ayhan, P.; Igdir, C.; Duygu, A. N. Enzyme catalyzed hydroxymethylation of aromatic aldehydes with formaldehyde. Synthesis of hydroxyacetophenones and (S)-benzoins. *Tetrahedron* **2004**, *60*, 6509–6512. (d) Demir, A. S.; Sesenoglu, O.; Dünkelmann, P.; Müller, M. Benzaldehyde lyase-catalyzed enantioselective carboligation of aromatic aldehydes with mono- and dimethoxy acetaldehyde. *Org. Lett.* **2003**, *5*, 2047–2050.

15 (a) Hildebrandt, G.; Klavehn, W. Manufacture of laevo-1-phenyl-2-methylaminopropanol-1. U.S. 1956950, 1934. (b) Neuberg, C.; Ohle, H. Zur Kenntnis der Carboligase; IV Mitteilung: Weitere Feststellungen über die biosynthetische Kohlenstoffkettenverknüpfung beim Gärungsvorgange. *Biochem. Z.* **1922**, *128*, 610–618. (c) Neuberg, C.; Hirsch, J. Über ein Kohlenstoffketten knüpfendes Ferment (Carboligase). *Biochem. Z.* **1921**, *115*, 282–310.

16 (a) Smallridge, A. J.; Trewhella, M. A.; Willkinson, K. A. Methods for the synthesis of amines such as ephedrine and intermediates. U.S. 7176332 B2, 2007. (b) Smallridge, A. J.; Trewhella, M. A.; Willkinson, K. A. Yeast-based process for production of L-PAC. U.S. 7063969 B2, 2006.

17 Kühl, S.; Zehentgruber, D.; Pohl, M.; Müller, M.; Lütz, S. Process development for enzyme catalyzed asymmetric C-C bond formation. *Chem. Eng. Sci.* **2007**, *62*, 5201–5205.

18 Stillger, T.; Pohl, M.; Wandrey, C.; Liese, A. Reaction engineering of benzaldehyde lyase catalyzing enantioselective C-C bond formation. *Org. Proc. Res. Dev.* **2006**, *10*, 1172–1177.

19 (a) Mikolajek, R.; Spiess, A. C.; Pohl, M.; Lamare, S.; Büchs, J. An activity, stability and selectivity comparison of propioin synthesis by thiamine diphosphate-dependent enzymes in a solid/gas bioreactor. *ChemBioChem* **2007**, *8*, 1063–1070. (b) Mikolajek, R.; Spiess, A. C.; Büchs, J. Feasibility of gas/solid carboligation: conversion of benzaldehyde to benzoin using thiamine diphosphate-dependent enzymes. *J. Biotechnol.* **2007**, *129*, 723–725.

20 (a) Hischer, T.; Gocke, D.; Fernández, M.; Hoyos, P.; Alcántara, A. R.; Sinisterra, J. V.; Hartmeier, W.; Ansorge-Schumacher, M. B. Stereoselective synthesis of novel benzoins catalyzed by benzaldehyde lyase in a gel-stabilized two-phase system. *Tetrahedron.* **2005**, *61*, 7378–7383. (b) Kurleman, N.; Liese, A. Immobilization of benzaldehyde lyase and its application as a heterogeneous catalyst in the continuous synthesis of a chiral 2-hydroxy ketone. *Tetrahedron: Asymmetry* **2004**, *15*, 2955–2958.

21 (a) Domínguez de María, P.; Stillger, T.; Pohl, M.; Kiesel, M.; Liese, A.; Gröger, H.; Trauthwein, H. Enantioselective C-C bond ligation using recombinant *E. coli*-whole-cell biocatalysts. *Adv. Synth. Catal.* **2008**, *350*, 165–173. (b) Domínguez de María, P.; Trauthwein, H.; May, O.; Gröger, H.; Drauz, K. Process for preparing enantiomerically enriched α-hydroxy ketones. WO2006087266, 2006.

22 Gotor-Fernández, V.; Brieva, R.; Gotor, V. Lipases: Useful biocatalysts for the preparation of pharmaceuticals. *J. Mol. Catal. B: Enzym.* **2006**, *40*, 111–120.

23 Hoyos, P.; Domínguez de María, P.; Sinisterra, J. V.; Alcántara, A. R. Hydrolase-based synthesis of enantiopure α-hydroxy ketones: From racemic resolutions to chemo-enzymatic dynamic kinetic resolutions. *Biotechnology Research: Technology and Applications*; Nova Science Publishers, Inc.: New York, 2009; pp 97−119.

24 (a) Silva, D. J.; Kahne, D.; Kraml, C. M. Chromomycin A_3 as a blueprint for designed metal complexes. *J. Am. Chem. Soc.* **1994**, *116*, 2641–2642. (b) Tanyeli, C.; Demir, A. S.; Dikici, E. New chiral synthon from the PLE catalyzed enantiomeric separation of 6-acetoxy-3-methylcyclohex-2-en-1-one. *Tetrahedron: Asymmetry* **1996**, *7*, 2399–2402. (c) Kajiro, H.; Mitamura, S.; Mori, A.; Hiyama, T. Enantioselective synthesis of 2-hydroxy-1-indanone, a key precursor of enantiomercially pure 1-amino-2-indanol. *Tetrahedron: Asymmetry* **1998**, *9*, 907–910. (d) Demir, A. S.; Findik, H.; Köse, E. A new and efficient chemoenzymatic route to both enantiomers of α′-acetoxy-α-methyl and γ-hydroxy-α-methyl cyclic enones. *Tetrahedron: Asymmetry* **2004**, *15*, 777–781. (e) Tanyeli, C.; Ozdemirhan, F.; Iyigun, C. The first enzymatic resolution of quaternary α′-acetoxy α,β-unsaturated cyclohexenones and cyclopentenones. *Tetrahedron: Asymmetry* **2005**, *16*, 4050–4055. (f) Tanyeli, C.; Akhmedov, I.; Iyigun, C. The first enzymatic resolution of quaternary α-acetoxy α-substituted cyclic ketones. *Tetrahedron: Asymmetry* **2006**, *17*, 1125–1128.

25 (a) Adam, W.; Diaz, M. T.; Saha-Möller, C. Lipase-catalyzed kinetic resolution of α,β-unsaturated α′-acetoxy ketones. *Tetrahedron: Asymmetry* **1998**, *9*, 791–796. (b) Wessjohann, L. A.; Scheid, G.; Bornscheuer, U. T.; Henke, E.; Kuit, W.; Orru R. Epothilone synthesis components III and IV: Asymmetrically substituted acyloins and acyloin derivatives, method for the production thereof and method for the productions of epothilone B and Epothilone derivatives. WO2002032844, 2002. (c) Scheid, G.; Ruijter, E.; Konarzycka-Bessler, M.; Bornscheuer, U. T.; Wessjohann, L. A. Synthesis and resolution of a key building block for epothilones: a comparison of asymmetric synthesis, chemical and enzymatic resolution. *Tetrahedron: Asymmetry* **2004**, *15*, 2861–2869. (d) Scheid, G.; Kuit, W.; Ruijter, E.; Orru, R. V.; Henke, E.; Bornscheuer, U. T.; Wessjohann, L. A. A new route to protected acyloins and their enzymatic resolution with lipases. *Eur. J. Org. Chem.* **2004**, 1063–1074.

26 (a) Ohta, H.; Ikemoto, M.; Il, H.; Okamoto, Y.; Tsuchihaschi, G. Preparation of optically active α-acetoxyacylophenones via enzyme mediated hydrolysis. *Chem. Lett.* **1986**, 1169–1172. (b) Gala, D.; DiBenedetto, D. J.; Clark, J. E.; Murphy, B. L.; Schumacher, D. P.; Steinman, M. Preparations of antifungal Sch 42427/SM 9164: Preparative chromatographic resolution, and total asymmetric synthesis via enzymatic preparation of chiral α-hydroxy arylketones. *Tetrahedron Lett.* **1996**, *37*, 611–614. (c) Demir, A. S.; Hamamci, H.; Tanyeli, C.; Akhmedov, I. M.; Doganel, F. Synthesis and *Rhizopus oryzae* mediated enantioselective hydrolysis of α-acetoxy aryl alkyl ketones. *Tetrahedron: Asymmetry* **1998**, *9*, 1673–1677. (d) Demir, A. S.; Hamamci, H.; Sesenoglu, O.; Aydogan, F.; Capanoglu, D.; Neslihanoglu, R. Simple chemoenzymatic access to enantiopure pharmacologically interesting (*R*)-2-hydroxypropiophenones. *Tetrahedron: Asymmetry* **2001**, *12*, 1953–1956. (e) Jeon, N. Y.; Ko, S. J.; Lee, Y. S.; Kim, B. T.; Won, K.; Lee, H. Synthesis of optically pure halogenated phenyl 2-hydroxypropanones by lipase-catalyzed enantioselective transesterification. *J. Mol. Catal. B: Enzym.* **2007**, *48*, 38–41.

27 (a) Aoyagi, Y.; Agata, N.; Shibata, N.; Horiguchi, M.; Williams, R. M. Lipase TL®-mediated kinetic resolution of benzoin: facile synthesis of (1*R*,2S)-erythro-2-amino-1,2-diphenylethanol. *Tetrahedron Lett.* **2000**, *41*, 10159–10162. (b) Aoyagi, Y.; Iijima, A.; Williams, R. M. Asymmetric synthesis of [2,3-$^{13}C_2$,^{15}N]-4-Benzyloxy-5,6-diphenyl-2,3,5,6-tetrahydro-4H-oxazine-2-one via lipase TL-mediated kinetic resolution of benzoin: General procedure for the synthesis of [2,3-$^{13}C_2$,^{15}N]-L-Alanine. *J. Org. Chem.* **2001**, *66*, 8010–8014.

28 (a) Pàmies, O.; Bäckvall, J.-E. Chemo-enzymatic dynamic kinetic resolution. *Trends Biotechnol.* **2004**, *22*, 130–135. (b) Martín-Matute, B.; Bäckvall, J.-E. Dynamic kinetic resolution catalyzed by enzymes and metals. *Curr. Opin. Chem. Biol.* **2007**, *11*, 226–232. (c) Pellisier, H. Recent developments in dynamic kinetic resolution. *Tetrahedron* **2008**, *64*, 1563–1601.

29 Taniguchi, T.; Ogasawara, K. Lipase-triethylamine-mediated dynamic transesterification of a tricyclic acyloin having a latent meso-structure: a new route to optically pure oxodicyclopentadiene. *Chem. Commun.* **1997**, 1399–1400.

30 Ödman, P.; Wessjohann, L. A.; Bornscheuer, U. T. Chemoenzymatic dynamic kinetic resolution of acyloins. *J. Org. Chem.* **2005**, *70*, 9551–9555.

31 (a) Ahn, Y.; Ko, S.; Kim, M. J.; Park, J. Racemization catalysts for the dynamic kinetic resolution of alcohols and amines. *Coord. Chem. Rev.* **2008**, *252*, 647–658. (b) Bogár, K.; Hoyos, P.; Alcántara, A. R.; Bäckvall, J.-E. Chemoenzymatic dynamic kinetic resolution of sterically hindered allylic alcohols under mild conditions: A synthetic route to enantiomerically enriched acyloin acetates. *Org. Lett.* **2007**, *9*, 3401–3404.

32 Hoyos, P.; Fernández, M.; Sinisterra, J. V.; Alcántara, A. R. Dynamic kinetic resolution of benzoins by lipase-metal combo catalysis. *J. Org. Chem.* **2006**, *71*, 7632–7637.

33 Hoyos, P.; Buthe, A.; Ansorge-Schumacher, M. B.; Sinisterra, J. V.; Alcántara, A. R. Highly efficient one pot dynamic kinetic resolution of benzoins with entrapped *Pseudomonas stutzeri* lipase. *J. Mol. Catal. B: Enzym.* **2008**, *52*−*53*, 133–139.

34 (a) Carballeira, J. D.; Quezada, M. A.; Hoyos, P.; Simeó, Y.; Hernaiz, M. J.; Alcántara, A. R.; Sinisterra, J. V. Microbial cells as catalysts for stereoselective red-ox reactions. *Biotechnol. Adv.* **2009**, *27*, 686–714. (b) Gamenara, D.; Domínguez de María, P. *Candida* spp. redox machineries: An ample biocatalytic platform for practical applications and academic insights. *Biotechnol. Adv.* **2009**, *27*, 278–285. (c) Goldberg, K.; Schroer, K.; Lütz, S.; Liese, A. Biocatalytic ketone reduction—a powerful tool for the production of chiral alcohols—Part II: whole-cell reductions. *Appl. Microbiol. Biotechnol.* **2007**, *76*, 249–255. (d) Goldberg, K.; Schroer, K.; Lütz, S.; Liese, A. Biocatalytic ketone reduction—a powerful tool for the production of chiral alcohols—Part I: processes with isolated enzymes. *Appl. Microbiol. Biotechnol.* **2007**, *76*, 237–248. (e) De Wildeman, S. M. A.; Sonke, T.; Schoemaker, H. E.; May, O. Biocatalytic reductions: From lab curiosity to first choice. *Acc. Chem. Res.* **2007**, *40*, 1260–1266.

35 Gröger, H.; Chamouleau, F.; Orologas, N.; Rollmann, C.; Drauz, K. H.; Waldmann, H.; Hummel, W.; Weckbecker, A.; May, O. Enantioselective reduction of ketones with "designer cells" at high substrate concentrations: highly efficient access to functionalized optically active alcohols. *Angew. Chem., Int. Ed.* **2006**, *45*, 5677–5681.

36 Bel-Rhlid, R.; Fauve, A.; Veschambre, H. Synthesis of pheromone components of the grape borer *Xylotrechus pyrrhoderus* by microbiological reduction of an α-diketone. *J. Org. Chem.* **1989**, *54*, 3221–3223.

37 (a) Hoyos, P.; Sansottera, G.; Fernández, M.; Molinari, F.; Sinisterra, J. V.; Alcántara, A. R. Enantioselective monoreduction of different 1,2-diaryl-1,2-diketones catalysed by lyophilised whole cells from *Pichia glucozyma*. *Tetrahedron* **2008**, *64*, 7929–7936. (b) Demir, A. S.; Ayhan, P.; Demirtaş, U.; Erkılıç, U. *Fusarium roseum* and *Aspergillus oryzae*-mediated enantioselective reduction of benzyls to benzoins. *J. Mol. Catal. B: Enzym.* **2008**, *55*, 164–168. (c) Saito, T.; Maruyama, R.; Ono, S.; Yasukawa, N.; Kodaira, K.; Nishizawa, M.; Ito, S.; Inoue, M. Asymmetric reduction of benzyl to (*S*)-benzoin with whole cells of *Bacillus cereus*. *Appl. Biochem. Biotechnol.* **2003**, *111*, 185–190. (d) Matsuda, T.; Harada, T.; Nakajima, N.; Nakamura, K. Mechanism for improving stereoselectivity for asymmetric reduction using acetone powder of microorganism. *Tetrahedron Lett.* **2000**, *41*, 4135–4138. (e) Matsuda, T.; Harada, T.; Nakajima, N.; Itoh, T.; Nakamura, K. Two classes of enzymes of opposite stereochemistry in an organism: One for fluorinated and another for Nonfluorinated substrates. *J. Org. Chem.* **2000**, *65*, 157–163. (f) Bortolini, O.; Fantin, G.; Fogagnolo, M.; Giovannini, P.; Guerrini, G.; Medici, A. An easy approach to the synthesis of optically active *vic*-Diols: A new single-enzyme system. *J. Org. Chem.* **1997**, *62*, 1854–1856. (g) Chênevert, R.; Thiboutot, S. Baker's Yeast Reduction of 1,2-Diketones. Preparation of Pure (*S*)-(−)-2-Hydroxy-1-phenyl-1-propanone. *Chem. Lett.* **1988**, 1191–1192. (h) Konishi, J.; Ohta, H.; Tsuchihashi, G. Asymmetric reduction of benzyl to benzoin catalyzed by the enzyme system of a microorganism. *Chem. Lett.* **1985**, 1111–1112.

38 (a) Mahmoodi, N. O.; Navrood, M. N. Enantio-, regio-, and chemoselective reduction of aromatic a-diketones by baker's yeast in diverse organic-water solvent. *ARKIVOC* **2007**, *iii*, 37–45. (b) Mahmoodi, N. O.; Mohammadi, H. G. Enantio-, regio-, and chemoselective reduction of aromatic a-diketones by baker's yeast. *Monatsh. Chem.* **2003**, *134*, 1283–1288. (c) Nakamura, K.; Kondo, S.; Kawai, Y.; Hida, K.; Kitano, K.; Ohno, A. Enantio- and regioselective reduction of α-diketones by baker's yeast. *Tetrahedron: Asymmetry* **1996**, *7*, 409–412.

39 Maruyama, R.; Nishizawa, M.; Itoi, Y.; Ito, S.; Inoue, M. Isolation and expression of a *Bacillus cereus* gene encoding benzyl reductase. *Biotechnol. Bioeng.* **2001**, *75*, 630–633.

40 Bortolini, O.; Casanova, E.; Fantin, G.; Medici, A.; Poli, S.; Hanau, S. Kinetic resolution of *vic*-diols by *Bacilus stearothermophilus* diacetyl reductase. *Tetrahedron: Asymmetry* **1998**, *9*, 647–651.

41 (a) Molinari, F. Oxidations with isolated and cell-bound dehydrogenases and oxidases. *Curr. Org. Chem.* **2006**, *10*, 1247–1263. (b) Sello, G.; Orsini, F. Alcohol and 1,2-diol dehydrogenases: Synthetic use in the preparation of chiral alcohols by carbonyl reduction. *Mini-Rev. Org. Chem.* **2006**, *3*, 11–21.

42 (a) Landis, B. H.; McLaughlin, J. K.; Heeren, R.; Grabner, R. W.; Wang, P. T. Bioconversion of *N*-Butylglucamine to 6-Deoxy-6-butylamino Sorbose by *Gluconobacter oxydans*. *Org. Proc. Res. Dev.* **2002**, *6*, 547–552. (b) Schroder, T.; Stubbe, M. Process for the preparation of 1-desoxynojirimycine and of its N-derivatives. US4806650, 2002. (c) Kinast, G.; Schedel, M. A four-step synthesis of 1-deoxynojirimycin with a biotransformation as cardinal reaction step. *Angew. Chem., Int. Ed.* **1981**, *20*, 805–806. (d) Reichstein, T.; Grüssner, A. Eine ergiebige Synthese der l-Ascorbinsäure. *Helv. Chim. Acta* **1934**, *17*, 311–328.

43 Romano, A.; Gandolfi, R.; Nitti, P.; Rollini, M.; Molinari, F. Acetic acid bacteria as enantioselective biocatalyst. *J. Mol. Catal. B: Enzym.* **2002**, *17*, 235–240.

44 Steinreiber, J.; Faber, K.; Griengl, H. De-racemization of enantiomers versus de-epimerization of diastereomers-classification of dynamic kinetic asymmetric transformations (DYKAT). *Chem.—Eur. J.* **2008**, *14*, 8060–8072.

45 (a) Demir, A. S.; Hamamci, H.; Ayhan, P.; Duygu, A. N.; Igdir, A. C.; Capanoglu, D. Fungi mediated conversion of benzyl to benzoin and hydrobenzoin. *Tetrahedron: Asymmetry* **2004**, *15*, 2579–2582. (b) Demir, A. S.; Hamamci, H.; Sesenoglu, O.; Neslihanoglu, R.; Asikoglu, B.; Capanoglu, D. Fungal deracemization of benzoin. *Tetrahedron Lett.* **2002**, *43*, 6447–6449.

46 (a) Nestl, B. M.; Bodlenner, A.; Stuermer, R.; Hauer, B.; Kroutil, W.; Faber, K. Biocartalytic racemization of synthetically important functionalized α-hydroxy ketones using microbial cells. *Tetrahedron: Asymmetry* **2007**, *18*, 1465–1474. (b) Nestl, B. M.; Voss, C. V.; Bodlenner, A.; Ellmer-Schaumberger, U.; Kroutil, W.; Faber, K. Biocatalytic racemization of *sec*-alcohols and α-hydroxy ketones using lyophilized microbial cells. *Appl. Microbiol. Biotechnol.* **2007**, *76*, 1001–1008.