Acc. Chem. Res. **1999,** *32,* 837−845

Biocatalytic Synthesis of Optically Active α-Oxyfunctionalized Carbonyl Compounds

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Received July 27, 1998

The present Account covers the recent progress in the biocatalytic formation of optically active α-oxyfunctionalized carbonyl compounds, in particular, the α-hydroxy, α-hydroperoxy and α-acetoxy derivatives of aldehydes, ketones, carboxylic acids, and esters, which constitute valuable synthetic building blocks in preparative organic chemistry. The important enzymatic methods available to date are summarized in Scheme 1, in which the enantioenriched, α-oxyfunctionalized carbonyl products have been obtained either through kinetic resolution of racemates or by asymmetric induction of prochiral substrates. Instead of substrate oriented, Scheme 1 is classified in terms of the various enzyme types, which have been successfully employed for the syntheses of optically active α-oxyfunctionalized carbonyl compounds. The scheme has been arranged in the form of a rosette, and the coverage shall be in the clockwise sense. We find this focus most effective in bringing across the utility and efficacy of the enzymatic transformations presented herein.

Introduction

Enantiomerically pure compounds are becoming increasingly more important in the production of pharmaceuticals, agrochemicals (e.g., pesticides, fungicides, herbicides), and flavors. For example, the world market for single-isomer chiral drugs amounted to ca. 73 billion U.S. dollars in 1996, and in the year 2000 this will increase to 90 billion.[1] Therefore, the development of efficient and environmentally acceptable processes for the preparation of optically active substrates is essential, but still presents a major challenge in organic synthesis.

Of the numerous methods which have been developed in the past decades for the preparation of optically active compounds, the biocatalytic processes are becoming more and more popular for this purpose.[2] The reasons for the increasing acceptance of enzymes by organic chemists as synthetic tool rest on the advantages gained from utilizing them in asymmetric synthesis. Isolated or whole-cell enzymes are efficient catalysts under mild reaction conditions. Since enzymes are chiral materials, optically active substances may be produced in high enantiomeric excess from prochiral or racemic substrates by catalytic asymmetric induction or kinetic resolution. A special case of prochiral substrates entails the enzymatic asymmetrization of *meso* compounds to afford enantiomerically enriched products. Furthermore, enzymes, in particular, hydrolases (e.g., lipases, proteases), exhibit catalytic activities in organic media, which facilitate enzymatic transformations of hydrophobic substrates.[3] Moreover, biocatalysts are environmentally compatible, and they may perform transformations, which are difficult to emulate by chemical catalysts.

Optically active α-oxyfunctionalized carbonyl compounds, in particular, carboxylic acids,[4] aldehydes,[5] and ketones,[6] are indispensable building blocks for asymmetric synthesis due to their versatile functional groups, which may be easily transformed to other functionalities, e.g., diols, halo or amino derivatives, and epoxides. Indeed, optically active α-hydroxy acids or ketones have been successfully utilized as starting materials for the asymmetric synthesis of a variety of biologically active molecules; a small selection is depicted in Figure 1.[7] Clearly, the convenient and efficient synthesis of optically active α-hydroxy carbonyl compounds is of timely significance and in urgent demand.

Several chemical methods have been developed for the synthesis of optically active α-oxyfunctionalized carbonyl compounds.[8−10] Alternative to the chemical methods, these chiral substrates may be prepared in high enantioselectivities enzymatically. In the last few years we have reported[11−17] on several efficient, biocatalytic methods for the preparation of optically active α-oxyfunctionalized

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Michael Lazarus, born in 1969 in Germany, commenced his food chemistry studies in 1990 at the University of Würzburg. In 1998 he received his doctoral degree under the joint supervision of Professors Adam and Schreier. His doctoral work on the biocatalytic synthesis of optically active 2-hydroxy acids and the HRP-catalyzed kinetic resolution of hydroperoxides forms the basis of this Account.

Chantu R. Saha-Möller was born in 1955 in Bangladesh and received his higher education in Germany (Dr. rer. nat. 1986, University of Hamburg, with W. Walter). In 1986−1987 he worked as postdoctoral associate with E. Block (SUNY Albany, NY) and subsequently joined W. Adam's research group (University of Würzburg) as research associate. In 1994 he accepted a permanent research position and is coauthor of over 90 scientific publications.

Peter Schreier, born in Poland, was educated in Germany (Dr. rer. nat. 1971, University of Karlsruhe) and started his academic career in 1976 at the Technical University of Munich. In 1980 he was appointed to the Chair of Food Chemistry at the University of Würzburg. He is coauthor/editor of over 10 monographs and well over 300 scientific publications.

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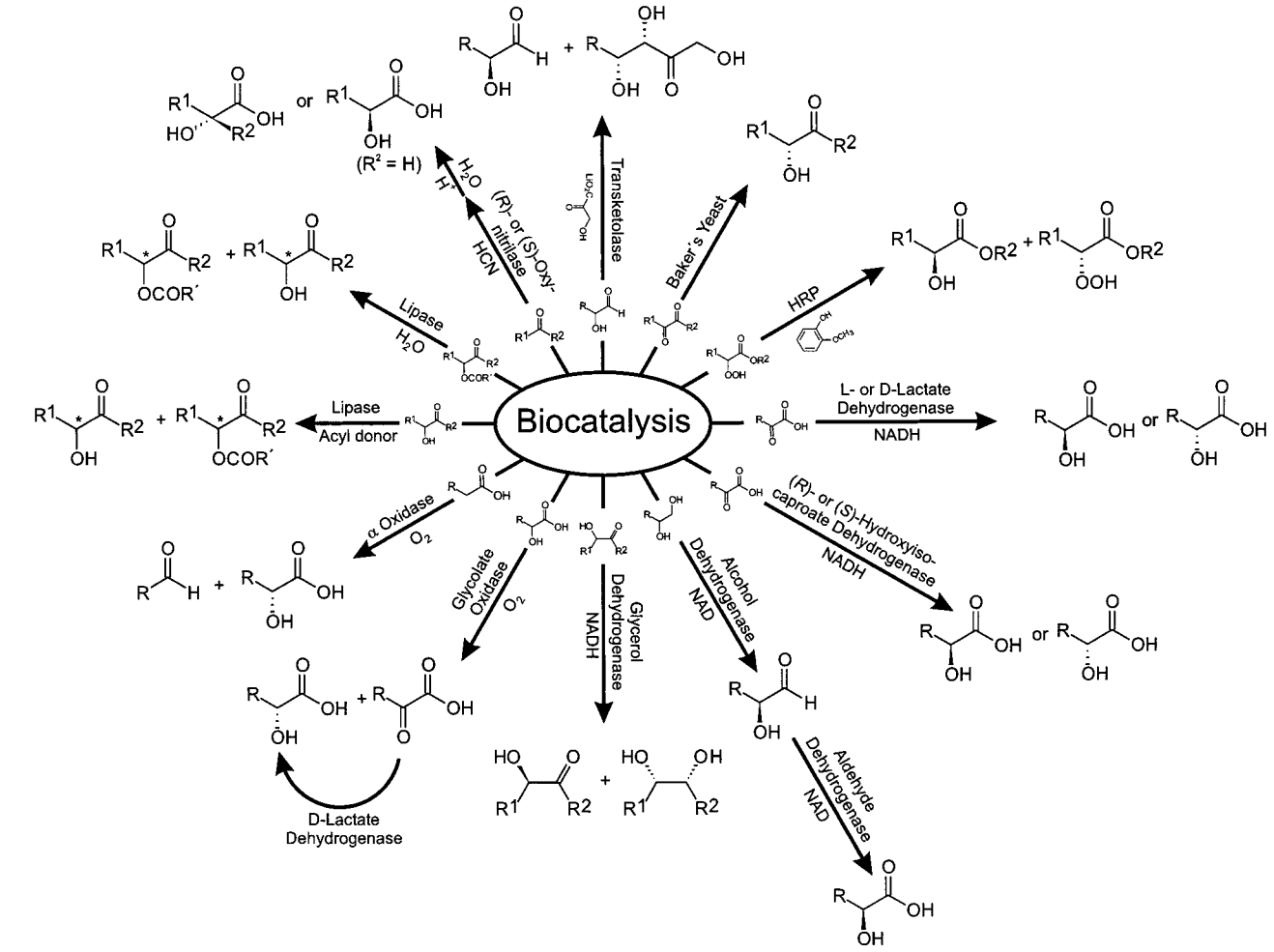
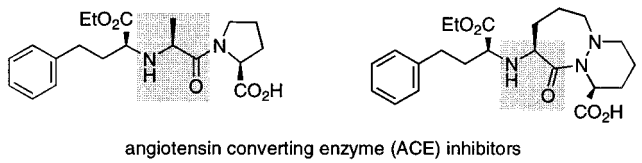
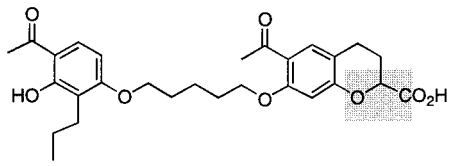
10.1021/ar980062i CCC: $18.00
Published on Web 02/17/1999

Scheme 1. Biocatalytic Synthesis of α-Oxyfunctionalized Carbonyl Compounds

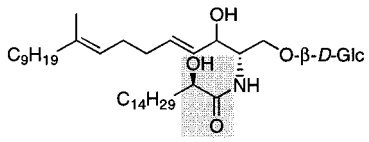




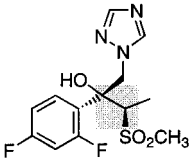
angiotensin converting enzyme (ACE) inhibitors



leukotriene antagonist



fruiting-inducing cerebroside
in *Schizophyllum commune*



antifugal activity

FIGURE 1. Selection of biologically active molecules prepared from optically active α-oxyfunctionalized carbonyl building blocks.

compounds. These chiral building blocks have been accessible by utilizing oxidoreductases (peroxidases, dehydrogenases, and oxidases), hydrolases (lipases), and lyases (oxynitrilases and transketolases). Here we present an overview of the recent development in biocatalytic synthesis of optically active α-oxyfunctionalized carbonyl compounds for asymmetric synthesis, with major emphasis on our own research efforts.

Enzymatic Synthesis of α-Oxyfunctionalized Carbonyl Compounds

Baker's Yeast. Fermentations of organic molecules by yeast were the first biotransformations described in the literature.[18] A broad spectrum of baker's yeast-mediated hydrolyses, oxidations, and reductions of organic substrates have been reported.[18] For example, this cellular enzyme system has been successfully employed for the synthesis of optically active α-hydroxy ketones and esters by asymmetric reduction of α-diketones and α-keto esters (Scheme 1, 1 o'clock; R^1= CH_3, C_2H_5, furanyl; R^2= C_6H_5, *p*-$CH_3OC_6H_4$, OCH_3, OC_2H_5).[19,20] However, the synthesis of optically active 2-hydroxy acids is not possible by baker's yeast since α-keto acids decarboxylate to the next lower aldehyde or alcohol.[21]

Oxidoreductase. Oxidoreductases are efficient biocatalysts for the selective oxidation and reduction of numerous organic substrates. These redox enzymes have received much attention in the last few years as chiral catalysts for synthetic applications. Three different types of oxidoreduc-

Table 1. Enantioselectivities of the HRP-Catalyzed Kinetic Resolution of Hydroperoxides in the Presence of Guaiacol[a]

entry	ROOH	ROOH ee (%)	ROH ee (%)	E[b]	lit.
1		97 (*R*)	97 (*S*)	>200	11
2		79 (*R*)	64 (*S*)	10.7	11
3		97 (*S*)	>99 (*R*)	>200	25
4		>99 (*S*)	>99 (*R*)	>200	25

[a] The enantiomeric excess was determined by HPLC analysis. [b] Enantiomeric ratio (ref 24).

tases, namely, peroxidases, dehydrogenases, and oxidases, have been used as biocatalysts for the asymmetric synthesis of α-oxyfunctionalized carbonyl compounds.

Peroxidases are heme-containing enzymes which oxidize a variety of structurally diverse substrates by using hydrogen peroxide or hydroperoxides as oxygen sources.[22] During the last few years, we have investigated the enzymatic kinetic resolution of racemic hydroperoxides by horseradish peroxidase (HRP) as the biocatalyst.[23] Thus, for the first time, *n*-alkyl derivatives of α- and *β*-hydroperoxy esters (Table 1) have been reduced by HRP in the presence of guaiacol to the respective hydroxy esters in excellent enantiomeric excess;[11,25] the case for the α derivatives is illustrated in Scheme 1 (2 o'clock). Branched alkyl groups exert an unfavorable influence on the stereoselectivity of this enzymatic reduction. For example, when the substituent at the chirality center of the α-hydroperoxy ester is changed from ethyl to isopropyl (Table 1, entries 1 and 2), the ee values decrease significantly, while a *tert*-butyl group prevents the enzymatic reduction entirely (data not shown). For the α-methylene *β*-hydroperoxy esters (entries 3 and 4), already the isopropyl derivative is not accepted by the HRP. These results demonstrate impressively the steric restrictions at the active site of the HRP enzyme.

Dehydrogenases are non-heme redox enzymes which catalyze hydrogen-transfer reactions in the presence of a coenzyme as hydrogen donor or acceptor. A number of different dehydrogenases have been utilized for the asymmetric reduction of carbonyl functionalities. For example, the L-lactate dehydrogenase (L-LDH, EC 1.1.1.27) catalyzes the enantioselective reduction of 2-oxo acids by NADH to the corresponding (*S*)-2-hydroxy acids and accepts a broad spectrum of substrates (Scheme 1, 3 o'clock; R = H, CH_3, $ClCH_2$, $HOCH_2$, $HSCH_2$, HOOC, $HOOCCH_2$, CH_3COCH_2, $CH_3SCH_2CH_2$, $C_6H_5CH_2$, cyclopropyl-CH_2, imidazolyl-CH_2, $CH_2{=}CHCH_2CH_2$, $CH_2{=}CH(CH_2)_2CH_2$).[26−28] The D-lactate dehydrogenase (D-LDH, EC 1.1.1.28), which is the complementary enzyme to the L-lactate dehydrogenase, reduces 2-oxo acids to the corresponding (*R*)-2-hydroxy acids in high enantioselectivity, but the substrate spectrum is substantially narrower than that of L-LDH.[29]

Like LDH, the D- and L-hydroxyisocaproate dehydrogenases from *Lactobacillus casei* (D-HicDH)[30] or *Lactobacillus confusus* (L-HicDH)[31] reduce 2-oxo acids to the corresponding (*R*)- or (*S*)-hydroxy acids; conversely, they oxidize selectively the (*R*)- or (*S*)-hydroxy acids to the corresponding keto acids (Scheme 1, 4 o'clock). These NAD-dependent oxidoreductases accept a variety of alkyl-substituted substrates (R = CH_3, CH_3CH_2, $CH_3CH_2CH_2$, $CH_3(CH_2)_2CH_2$, $(CH_3)_2CHCH_2$, $CH_3CH_2CH(CH_3)$, $CH_3(CH_2)_4$-CH_2, $C_6H_5CH_2$, *p*-$HOC_6H_4CH_2$, $HOCH_2$, $BrCH_2$, CH_3SCH_2-CH_2, indole-3-CH_2, imidazolyl-CH_2). They may possess a substrate selectivity similar to that of the enzyme LDH, but the hydroxyisocaproate dehydrogenases prefer substrates with longer side chains.

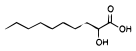
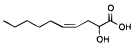
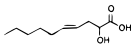
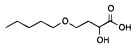
The NAD-dependent horse liver alcohol dehydrogenase[32] (HLADH, EC 1.1.1.1) catalyzes the highly enantioselective oxidation of 1,2-diols to (*S*)-2-hydroxy aldehydes (Scheme 1, 5 o'clock; R = CH_3, $HOCH_2$, FCH_2, $ClCH_2$, $BrCH_2$, H_2NCH_2, $CH_2{=}CH$, CH_3CH_2).[33] The reaction is thermodynamically unfavorable and requires NAD as cosubstrate. To circumvent this problem, the resulting α-hydroxy aldehyde is irreversibly converted *in situ* to the (*S*)-α-hydroxy acid with aldehyde dehydrogenase (AldDH, EC 1.2.1.5).[33]

The NAD-dependent glycerol dehydrogenases (GDH, EC 1.1.1.6) from *Enterobacter aerogenes* or *Cellulomonas species*, which possess quite different substrate selectivity in comparison to HLADH, catalyze the interconversion of 1,2-diols and α-hydroxy ketones (Scheme 1, 6 o'clock).[34] Therefore, this enzyme provides optically active α-hydroxy ketones either by the kinetic resolution of racemic α-hydroxy ketones [R_1 = R_2 = CH_3, $(CH_2)_3$] through *R*-enantioselective reduction or by the stereoselective oxidation of *cis*-1,2-diols [R_1,R_2 = $(CH_2)_4$]. Although the enzyme glycerol dehydrogenase, which requires an inert atmosphere, accepts acyclic and cyclic substrates, its inhibition by reaction products limits the synthetic application of this biocatalyst.

The glycolate oxidase (GOX, EC 1.1.3.15) is a peroxisomal enzyme, which is found in the leaves of many green plants and in the liver of mammalians,[35] and has already been expressed in genetically manipulated microorganisms.[36] This extensively studied enzyme converts *in vivo* glycolic acid to glyoxylic acid in the presence of molecular oxygen. We have recently employed this transformation for the unprecedented enzymatic resolution of racemic 2-hydroxy acids by the efficient enantioselective oxidation with the glycolate oxidase from spinach (*Spinacia oleracea*) to afford enantiomerically pure (*R*)-2-hydroxy acids (Scheme 1, 7 o'clock).[12] The enzyme oxidizes not only short-chain 2-hydroxy acids (Table 2, entries 1 and 4) but also longer-chain derivatives (entries 6−9). In contrast, the 2-hydroxy acids such as mandelic acid, 2-hydroxyisobutyric acid, and 2,3-dihydroxybutyric acid, with substantial steric demand in close proximity to the α-hydroxy functionality, are not accepted by the oxidase (data not shown in Table 2).[12] However, phenyllactic acid was oxidized by molecular oxygen (Table 2, entry 10), but the oxidase activity was remarkably diminished.

The kinetic resolution of the racemate through enantioselective oxidation of the (*S*)-2-hydroxy acid to the corresponding 2-oxo acid provides only a maximum 50%

Table 2. Conversion of Racemic 2-Hydroxy Acids into (*R*)-2-Hydroxy Acids Catalyzed by the Glycolate Oxidase (Method A) and the D-Lactate Dehydrogenase (Methods B and C)[12, 13]

entry	substrate	method[a]	convn (%)	ee (%)
1		**A**	50	>99
2		**B**	90[b]	91
3		**C**	89[b]	>99
4		**A**	50	>99
5		**C**	85[b]	94
6		**A**	50	>99
7		**A**	50	>99
8		**A**	50	>99
9		**A**	47	86
10		**A**	45	81

[a] Method A: enzymatic resolution of the 2-hydroxy acids with glycolate oxidase. Method B: The D-LDH was added to the glycolate oxidase medium. Method C: The D-LDH was added to the mixture of acids **1** and **2**, which has been separated from the glycolate oxidase medium. [b] Yield of the isolated 2-hydroxy acid.

yield of the (*R*)-2-hydroxy acid. For economic reasons, it would be desirable to prepare the (*R*)-2-hydroxy acids quantitatively from their racemic precursors in such a biocatalytic process. For this purpose, we have coupled the glycolate-oxidase-catalyzed oxidation of racemic 2-hydroxy acids with the asymmetric reduction of 2-oxo acids by D-lactate dehydrogenase from *L. leichmanii* for the novel, high-yield oxidoreductive synthesis of (*R*)-2-hydroxy acids (Scheme 1, 7 o'clock).[13] Indeed, this biocatalytic tandem reaction enables the preparation of enantiomerically pure (*R*)-2-hydroxy acids from racemates in nearly quantitative yield (Table 2, entries 2, 3, and 5).

In higher plants[37] and simple organisms,[38] 2-hydroxy fatty acids are formed in the oxidative lipid metabolism by α oxidation of the corresponding acids.[37,39] The flavoprotein-catalyzed oxidation of fatty acids leads to an intermediary α-hydroperoxy acid (Scheme 2), which preferentially decarboxylates to the corresponding aldehyde (Scheme 2, path B) in competition with reduction to the 2-hydroxy acid (Scheme 2, path A).[37] Presumably, the 2-hydroperoxy acid is first converted to an intermediary α-peroxy lactone, which decomposes very fast to CO_2 and the aldehyde.[39] Recently, we have employed this enzymatic oxidation[14] for the novel synthesis of enantiomerically pure (*R*)-2-hydroxy acids from long-chain carboxylic acids with molecular oxygen (Scheme 1, 8 o'clock), catalyzed by the α oxidase of pea (*Pisum sativum*). The results in Table 3 show that a broad variety of saturated fatty acids with 7−16 carbon atoms (entries 1−6) and unsaturated fatty acids (entries 7−12) as well as heteroatom-containing (oxygen, sulfur) carboxylic acids (entries

Scheme 2. α Oxidation of Fatty Acids in Higher Plants

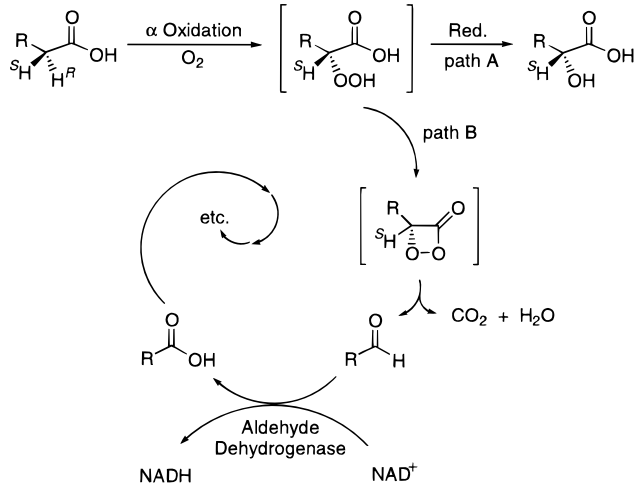
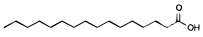
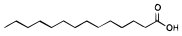
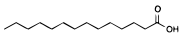
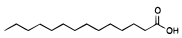
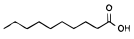
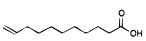
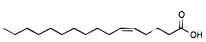
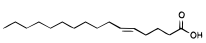
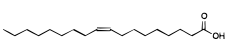
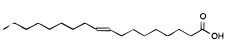
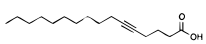
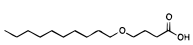
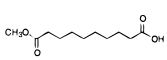
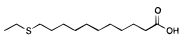
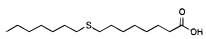


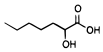
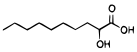
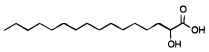
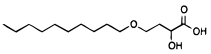
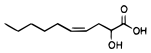
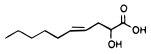
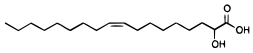
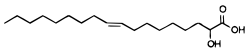
Table 3. α Hydroxylation of Carboxylic Acids by α Oxidase of Peas[14]

entry	substrate[a]	convn (%)	$RCHCO_2H$: RCHO (OH) (%)	ee (%)
1		46	40 : 60	>99
2		41	31 : 69	>99
3		100[b, c]	99 : 1	>99
4		100[b, c, d]	80 : 20	>99
5		33	48 : 52	>99
6		<10	e	>99
7		57	45 : 55	>99
8		10	20 : 80	>99
9		67	17 : 83	>99
10		86	24 : 76	>99
11		22	16 : 84	>99
12		<10	65 : 35	>99
13		87	49 : 51	>99
14		17	70 : 30	>99
15		100[b]	99 : 1	>99
16		100[b]	99 : 1	>99

[a] Crude homogenate of young pea leaves, 0.2 M phosphate buffer (pH 6.0), 0.1% Triton X-100; [b] Crude extract of germinating peas, 0.1 M Tris-HCl (pH 6.0). [c] SnCl2 was added as *in situ* reductant. [d] α-Oxidation was carried out with 0.5 mmol of myristic acid on the semipreparative scale. [e] Only the 2-hydroxy acid was detected as α-oxidation product.

13−16) are all well accepted by this α-oxidation enzyme system. However, when the triple and double bonds or a heteroatom are proximate (less than three carbon atoms) to the carboxylic acid functionality, the hydroxylation of such substrates does not take place. Furthermore, the more hydrophilic short-chain alkanoic acids (less than 7 carbon atoms) and dicarboxylic acids (data not shown in Table 3) are not converted by the α oxidase. Amazingly, thia-substituted acids yielded preferentially the enantio-

Table 4. Lipase-Catalyzed Kinetic Resolution of Racemic α-Hydroxy Carbonyl Substrates by Enantioselective Acetylation

entry	substrate	lipase[a]	acyl donor	solvent	time (h)	ROH ee (%)	ROAc ee (%)	E[b]	lit.
1		PSL	CH_2=C(CH_3)OAc	^{t}BuOMe	138	99 (*S*)	90 (*R*)	82	15
2		PSL	CH_2=C(CH_3)OAc	^{t}BuOMe	87	83 (*R*)	98 (*S*)	311	15
3		PSL	CH_2=C(CH_3)OAc	^{t}BuOMe	25	77 (*S*)	79 (*R*)	19	15
4		PSL	CH_2=C(CH_3)OAc	^{t}BuOMe	14	95 (*S*)	86 (*R*)	45	15
5		CAL	CH_2=CHOAc	^{t}BuOMe	48	62 (*R*)	56 (*S*)	6.5	16
6		BSL	CH_2=CHOAc	^{t}BuOMe	13	>98 (*R*)	80 (*S*)	40	16
7		CAL	CH_2=CHOAc	^{t}BuOMe	48	94 (*R*)	77 (*S*)	26	16
8		CAL	CH_2=CHOAc	^{t}BuOMe	48	>98 (*R*)	85 (*S*)	55	16
9		CAL	CH_2=CHOAc	^{t}BuOMe	48	>98 (*R*)	73 (*S*)	28	16
10		BSL	CH_2=CHOAc	^{t}BuOMe	3	91 (*R*)	98 (*S*)	>200	16
11		BSL	CH_2=CHOAc	^{t}BuOMe	6	89 (*R*)	98 (*S*)	>200	16
12		BSL	CH_2=CHOAc	^{t}BuOMe	2	65 (*R*)	43 (*S*)	4.7	16
13		CAL	CH_2=CHOAc	^{t}BuOMe	48	84 (*R*)	56 (*S*)	9	16
14		BSL	CH_2=CHOAc	^{t}BuOMe	2	70 (*R*)	62 (*S*)	8.7	16
15		BSL	CH_2=CHOAc	^{t}BuOMe	2	>99 (*R*)	75 (*S*)	34	16
16		BSL	CH_2=CHOAc	^{t}BuOMe	4	>98 (*R*)	80 (*S*)	40	16

[a] Lipase from *P. species* (PSL), *C. antarctica* (CAL) and *Burkholderia* sp. (BSL). [b] Enantiomeric ratio (ref 24).

merically pure 2-hydroxy acids at complete conversion (entries 15 and 16); not even traces of sulfoxidation were observed, despite the ease of oxidation of the sulfide functionality.[40]

Extensive screening revealed that the α-oxidation activity could be substantially improved by employing the crude extract of germinating peas rather than the homogenate from leaves.[14b] A major breakthrough for preparative-scale applications was the use of tin(II) chloride as *in situ* reducing agent,[41] which produces preferentially the 2-hydroxy acid by reduction of the intermediary α-hydroperoxy acids (path A in Scheme 2). Thereby, the competitive decarboxylation (path B in Scheme 2) of the 2-hydroperoxy acids to the aldehyde was circumvented (entries 3 and 4) and for the first time a biocatalytic α hydroxylation of carboxylic acids has been made available on the semipreparative scale for the direct synthesis of enantiopure 2-hydroxy acids in high yields. The enantioselectivity of this α oxidation originates from the stereoselective oxyfunctionalization of the α-methylenic C−H^R bond in the carboxylic acids by the α oxidase (Scheme 2). [14b]

Hydrolases. Lipases (EC 3.1.1.3) have been frequently used as convenient, efficient, and economical biocatalysts for the asymmetric synthesis of a wide range of organic compounds.[2] The advantages of these enzymes are that they do not require any expensive and labile cofactors or the sophisticated technology of recycling. Therefore, the lipase-catalyzed, irreversible transesterification with an acyl donor in organic media provides also a popular biocatalytic method for the preparation of optically active α-oxyfunctionalized carbonyl compounds (Scheme 1, 9 o'clock). Selective examples from our own group are shown in Table 4.

Pseudomonas lipases (PSL) are among the most useful enzymes for such biocatalytic transformations, which we have employed for the efficient enantioselective transesterification of racemic α-hydroxy ketones (Table 4, entries 1−4). The *R* enantiomer of the keto alcohol is recognized selectively by the enzyme PSL to result in the enantiomerically enriched (*R*)-keto acetate and (*S*)-keto alcohol, provided that the steric demand of the R^2 substituent is greater than that of R^1 (entries 1 and 2).

Also the acylation of long-chain 2-hydroxy acids affords the optically active α-hydroxy acids and their acetates in high enantiomeric excess, as has been demonstrated for 2-hydroxypalmitic acid.[42] Similarly, aromatic derivatives, e.g., methyl mandelate[43] and 2-hydroxy-4-phenylbutanoic acid,[44] may be resolved effectively by these enzymes. In a more detailed substrate-selectivity study,[16] we have shown that microbial lipases from *Candida antarctica* (CAL) and *Burkholderia species* (BSL) are efficient biocatalysts for the synthesis of optically active long- and short-chain saturated 2-hydroxy acids (Table 4, entries 6−10), as well as aromatic (entry 11) and unsaturated (entries 15 and 16) derivatives. However, the 2-hydroxy acids with a heteroatom (entry 12) or a double bond in close proximity (entries 13 and 14) to the α-hydroxy functionality show a significant decrease in the enantioselectivity of the microbial lipases. The short-chain 2-hydroxybutyric acid (entry 5) gave also a moderate enantiomeric excess on lipase-catalyzed acetylation. The reason for this lower substrate selectivity derives presumably from the fact that in the 2-hydroxybutyric acid the relative steric requirement of the ethyl substituent and the carboxylic functionality does not differ significantly enough to facilitate sufficient enantiodifferentiation by the enzyme. For comparison, excellent enantioselectivity was observed with the lipase BSL for the 2-hydroxyisovaleric acid, which possesses the sterically larger isopropyl substituent at the chirality center (entry 6).

Microbial lipases have also been used to effect the kinetic resolution of α-oxyfunctionalized carbonyl compounds by enantioselective hydrolysis of their esters (Scheme 1, 10 o'clock).[17,43,45,46] In this manner, we have obtained optically active α-hydroxy enones in excellent enantioselectivity from the corresponding α-keto acetates (Scheme 1, 10 o'clock; $R^1 = CH_3$, $R^2 = CH_2{=}CH$ or $CH_2{=}CCH_3$) with the lipase from the *Candida* species.[17]

Lyases. (*R*)- and (*S*)-cyanohydrins, which may be prepared in good yields and with high enantiomeric excess by enzyme-catalyzed addition of hydrogen cyanide to aldehydes in organic solvents, are hydrolyzed with concentrated hydrochloric acid without any racemization to the corresponding 2-hydroxy carboxylic acids (Scheme 1, 11 o'clock).[47] The (*R*)-oxynitrilase from *Prunus amygdalus* (EC 4.1.2.10) catalyzes the conversion of aliphatic, aromatic, and heterocyclic aldehydes and ketones to the corresponding (*R*)-cyanohydrins.[47] The complementary (*S*)-oxynitrilase from *Sorghum bicolor* (EC 4.1.2.11) catalyzes only the addition of hydrogen cyanide to aromatic and heterocyclic aldehydes to yield the corresponding (*S*)-cyanohydrins with an enantiomeric excess similar to that of the (*R*)-oxynitrilase; however, ketones and aliphatic aldehydes are not substrates for this enzyme.[47]

The thiamine pyrophosphate (TPP)- and magnesium-dependent transketolase from yeast (TK, EC 2.2.1.1), which is one of the enzymes in the pentose-phosphate biosynthetic pathway, catalyzes *in vivo* the transfer of the C_1-C_2 ketol unit from D-xylulose-5-phosphate to D-ribose-5-phosphate to generate D-sedoheptulose-7-phosphate (Scheme 1, 12 o'clock). This may be used in organic synthesis for the kinetic resolution of racemic 2-hydroxy aldehydes ($R = C_6H_5CH_2OCH_2$, CH_3OCH_2, $EtSCH_2$, FCH_2, CH_3CH_2, $CNCH_2$) by the selective reaction of the *R* enantiomer with lithium hydroxypyruvate to yield the corresponding 5-substituted 5-deoxy-D-xyluloses; left behind are the (*S*)-2-hydroxy aldehydes in good chemical yields and high enantiomeric excess.[48]

Concluding Remarks

Peroxidases, dehydrogenases, oxidases, lipases, oxynitrilases, and transketolases (Scheme 1) have been frequently used during the last few years as biocatalysts in the asymmetric synthesis of α-oxyfunctionalized carbonyl products. Although high enantioselectivities may be achieved in particular applications, some disadvantages must be pointed out for such biocatalytic methodology: Limited substrate spectrum and selectivity; enzyme availability, stability and cost; requirement of cosubstrates; recycling of coenzymes; enzyme inhibition; moderate yields (maximum 50%) of the required enantiomer in kinetic resolutions; availability of only one enantiomer. The methods of broadest scope and applicability are the lipase-catalyzed acylation of racemic α-hydroxy carbonyl substrates or the hydrolysis of racemic ester derivatives, which enables the synthesis of a wide range of optically active α-oxyfunctionalized carbonyl compounds, e.g., aldehydes, ketones, carboxylic acids, and esters. For the preparation of optically active α-hydroxy aldehydes and ketones, the lipase-catalyzed kinetic resolution of their racemates or protected racemic derivatives is superior to the transformation by the GDH enzyme or transketolase from yeast due to enzyme inhibition and narrow substrate specificity. Furthermore, in the case of baker's yeast, low product selectivity limits its synthetic utility. In contrast, dehydrogenases (LDH, HicDH), α oxidases, and oxynitrilases operate through asymmetric induction on prochiral aldehydes or ketones, carboxylic acids, and α-oxo acids and therewith make available the enantioenriched α-hydroxy acid quantitatively; however, a limited substrate spectrum applies. Optically active α-hydroxy acids are also accessible, despite the aforementioned disadvantages of kinetic resolution, by the oxidation of racemic 1,2-diols with dehydrogenases (HLADH/AldDH), or racemic α-hydroxy acids by glycolate oxidase and the reduction of racemic α-hydroperoxy esters by horseradish peroxidase. The enantioselective, catalytic hydroxylation of prochiral carboxylic acids by α oxidases with molecular oxygen constitutes to date the only direct asymmetric enzymatic oxyfunctionalization without recourse to transformation of the oxygen functionalities in the substrate.

As mentioned in the Introduction, quite a few chemical methods are available for the synthesis of optically active α-oxyfunctionalized carbonyl compounds.[8−10] Space limitations do not permit a comparison of all these methods with the biocatalytic processes described in this Account. Nevertheless, we briefly mention our own efforts in the development of chemical methods for the synthesis of optically active α-oxyfunctionalized carbonyl products. For

example, chiral titanium enolates of ketones may be oxidized enantioselectively to α-hydroxy carbonyl products by dimethyldioxirane.[10b] In comparison to the biocatalytic methods (Scheme 1, 1, 5, 6, and 9 o'clock), this chemical process is noncatalytic and significantly less enantioselective. Recently, we have shown that (salen)Mn(III)-catalyzed asymmetric oxidation of prochiral silyl enol ethers leads to α-hydroxy ketones in high enantioselectivities.[10c] Furthermore, the enantioselective oxidation of silyl enol ethers[10d] or *vic*-diols[10e] with optically active dioxirane afforded α-hydroxy ketones in moderate to good enantiomeric excess.

In the future, it is hoped that modern biotechnology may provide modified enzymes, as well as microbiological systems, with a wide range of substrate acceptibility to extend the scope of biocatalytic processes for the preparation of optically active α-oxyfunctionalized carbonyl products. In the meantime, the repertoire (Scheme 1) of biocatalytic tools is already sufficiently extensive and versatile to assist the synthetic chemist in the demanding synthesis of such optically active target molecules and offers an attractive and viable alternative to organic and metallorganic catalysts.

We appreciate the research spirit and the diligence of all colleagues who have contributed to this fascinating and lively research area. Our work was generously supported by the Deutsche Forschungsgemeinschaft (SFB 347, Selektive Reaktionen Metallaktivierter Moleküle), the Bayerische Forschungsstiftung (Bayerischer Forschungsverbund Katalyse-FORKAT), and the Fonds der Chemischen Industrie. We thank Boehringer Mannheim for the generous gift of enzymes.

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AR980062I