Lipases – Enzymes for Biocatalytic Asymmetric Synthesis

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Introduction

Lipases (triacylglycerol ester hydrolases, EC 3.1.1.3) are found in most organisms and are known to catalyze the hydrolysis of triglycerides in vivo.\(^1\)\(^,\)\(^2\) They are some of the most studied and used biocatalysts in organic synthesis today. The versatility and popularity of lipases is attributed to their high catalytic efficiency on a broad range of substrates, combined with high regioselectivity and chiral recognition,\(^2\) their high stability in organic solvents and at elevated temperatures,\(^2,\)\(^3\) the reversibility of their mode of action into ester synthesis,\(^2,\)\(^4\) their non-toxic and environmentally friendly nature,\(^5\) and finally, their low cost.

Lipases from many different species have been isolated and are commercially available in different preparations such as crude powders, lyophilisates, or immobilized on solid particles or resins. Many are of microbial origin, and advances in biotechnology have allowed production of lipases on a multi-ton scale using recombinant hosts.\(^2\)

In practice, lipases are very easy to handle and use. The principal reactions catalyzed by the enzymes are ester hydrolysis or synthesis, typically of acetates (Scheme 1). Hydrolysis is usually performed in a biphasic system consisting of an aqueous buffer and an organic solvent. Esterification is accomplished in an organic solvent with an irreversible acyl donor,\(^4\) such as the enol ester vinyl acetate. The enzyme is conveniently removed by filtration during work-up. The inherent chirality of the enzyme dictates a stereopreference of the reactions which can be exploited for asymmetric synthesis.

\[\text{lipase, acyl donor, organic solvent} \rightarrow \text{lipase, organic solvent / aqueous buffer} \]

Scheme 1 Principle reactions in synthesis catalyzed by lipases.

The applications of lipases in synthesis are diverse, and include resolution of racemates,\(^6\) hybrid metal–enzyme catalyzed dynamic kinetic resolution,\(^7\) desymmetrizations of prochiral or meso substrates\(^8\) and regioselective protective group manipulations.\(^9a,\)\(^b\)

Abstracts

(A) Kinetic resolution of racemates is the most common application for lipases in organic synthesis, and there are countless examples of successful attempts to separate enantiomers with a free hydroxyl residing not too far from the stereogenic center.\(^6\) The ee values are short of astonishing in many cases, and lipases are therefore very useful in the preparation of chiral synthons.\(^10\) Enantiomers of C\(_4\) building blocks featuring a dithiane and an oxirane were constructed by Sundby et al., with a lipase-catalyzed kinetic resolution as a key step.\(^11\)
(B) Integration of lipase-catalyzed kinetic resolution into a reaction sequence may be a rewarding solution in cases where stereoselective synthesis is unavailable or fails. Kamal et al. have developed a one-pot synthesis of enantiopure secondary alcohols from carbonyl compounds by tandem reduction–resolution.\(^{12a}\) The method was applied in a chemoenzymatic synthesis of both enantiomers of the \(\beta\)-adrenoreceptor blocker propranolol (1) in excellent yields and optical purities.\(^{12b}\)

(C) Yamagishi et al. reported a lipase-catalyzed kinetic resolution of \(\alpha\)-hydroxy-\(\alpha\)-phosphinates.\(^{13}\) With two chiral centers, one on phosphorus and one on the adjacent carbon, the substrate comprised a mixture of diastereomers. The lipase hydrolyzed the acetate of only one diastereomer in the mixture stereoselectively with very high preference, yielding one enantiomer in excellent ee.

(D) Lipases have become important tools for regio- and stereoselective protection and deprotection of carbohydrates.\(^{4}\) In a study on regioselective acylation of pyranoses, Gonçalves et al. unveiled enzymatic means for the resolution of \(\alpha\) and \(\beta\)-anomers of galactose derivatives.\(^{13}\) Both anomers were acylated in position 6, while the \(\beta\)-anomer reacted also on position 2.

(E) While kinetic resolution offers a maximum yield of 50% of one enantiomer, dynamic kinetic resolution (DKR) may realize higher yields of the desired enantiopure compound by constant racemization of the substrate in situ.\(^{7}\) Protocols for chemoenzymatic DKR of different substrates employing a metal catalyst for racemization and an immobilized lipase have been developed by Bäckvall and co-workers.\(^{7}\) Recently, a highly efficient method for DKR of alcohols was reported.\(^{15}\)

(F) Lipase-catalyzed enantioselective desymmetrization can afford optically active compounds in high yields since all of the substrate can be utilized in a symmetry-breaking reaction.\(^{7}\) In pursuit of axially chiral biaryls, Matsumoto et al. applied lipases to stereoselectively hydrolyze \(\sigma\)-symmetric biaryl diacetates.\(^{16}\)

(G) Desymmetrization of prochiral diols affords enantiomerically enriched mono-esters. 2-Functionalized 1,3-propanediols are useful starting materials for asymmetric acetylation with lipases, yielding products that can be further transformed with chemo-selectivity. Neri and Williams used lipases to desymmetrize N-Boc-serinol, and converted the product further into chiral Evans auxiliaries.\(^{17}\)

References

(10) Lipase enzymes are abbreviated with respect to the species of origin. For the exact preparation and trade name, please see the original reference.