Medicinal chemistry, Fine chemicals

Enantiodivergent synthesis of chiral compounds using a single enzyme

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Abstract

Many pharmaceuticals are optically active compounds. Since enantiomers of such compounds often exhibit distinct biological activities, the selective synthesis of each enantiomer represents one of the most fundamental challenges in medicinal chemistry. Enzymes have been widely employed in the synthesis of optically active compounds because of their excellent enantioselectivity. However, as enzymes are typically available only in one enantiomeric form, access to products with the opposite configuration remains limited.

This study presents a method for synthesizing both the (*R*)- and (*S*)-enantiomers of esters using a single lipase and the same starting material. Specifically, we developed an (*S*)-convergent transformation of racemic esters employing a native (*R*)-selective lipase. This transformation was accomplished by integrating three inherently incompatible reactions within a single system. The use of a Pickering emulsion enabled this integration by spatially compartmentalizing the reactions.

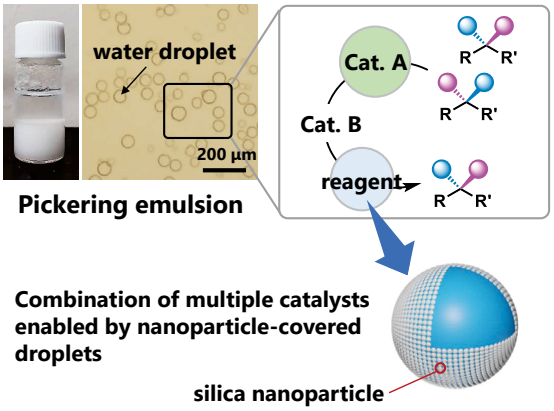
Background & Results

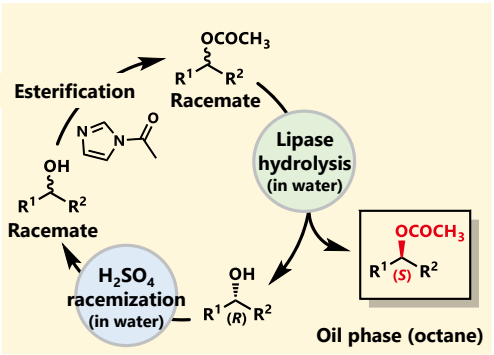
The chemical system within living cells represents the most efficient and environmentally benign modes of molecular transformation. In a single cell, various enzymes operate without mutual interference, allowing numerous reactions to proceed simultaneously. Such a sophisticated system is achieved through the compartmentalization of reaction media, in which enzymes are spatially separated by organelles. In this study, we developed cell-mimetic, compartmentalized reaction media based on Pickering emulsions stabilized by nanoparticles adsorbed at the oil–water interface. This approach enabled multiple reactions to occur simultaneously within a single system, thereby achieving an (*S*)-convergent transformation of racemic esters using a native (*R*)-selective lipase.

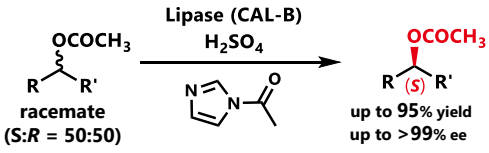
The (*S*)-convergent transformation of racemic esters was achieved by integrating three reactions: (1) lipase-catalyzed (*R*)-selective hydrolysis of a racemic ester, (2) H_2SO_4-catalyzed racemization of the resulting (*R*)-alcohol, and (3) esterification of the racemized alcohol. The formation of a Pickering emulsion containing lipase and H_2SO_4 in separate droplets enabled the compartmentalization of these reagents, thereby integrating three inherently incompatible reactions within a single system.

Significance of the research and Future perspective

Complementary to our previously reported (*R*)-convergent transformation, this approach enables the selective synthesis of both (*R*)- and (*S*)-enantiomers of optically active esters using a single lipase and the same starting material. These findings advance medicinal and pharmaceutical process chemistry by providing optically active compounds with high enantiomeric purity. Furthermore, this strategy is potentially applicable not only to other enzymes but also to various designer catalysts.







Patent	
Treatise	Nishio, Tomoya; Akai, Shuji; Kanomata, Kyohei. (S)-Convergent Deracemization of Racemic Esters with (R)-Selective Lipase: Pickering Emulsion Strategy for Enantiodivergent Synthesis Using a Native Enzyme. ACS Catalysis. 2025, 15(8), 6565–6571. doi: 10.1021/acscatal.4c07986 Kin, Takusho; Akai, Shuji; Kanomata, Kyohei et al. Dynamic kinetic resolution of tert-alcohols via combination of a lipase/Brønsted acid in a biphasic reaction medium. Green Chemistry. 2025, 27(32), 9672–9678. doi: 10.1039/D4GC06535B Moon, Jihoon; Akai, Shuji; Kanomata, Kyohei et al. Lipase/H_2SO_4-cocatalyzed dynamic kinetic resolution of alcohols in Pickering emulsion. ChemCatChem. 2023, 15(18), e202300878. doi: 10.1002/cctc.202300878
URL	https://handai-seizo.jp/?lang=en
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