Hydrolases in Process Chemistry: What Renders Hydrolase-Catalyzed Kinetic Resolution Industrially Viable?

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For hydrolase-catalyzed kinetic resolution to be viable on an industrial scale, at least three issues should be addressed in a practical manner which are as follows: (1) synthetically useful enantioselectivity ($E > 20$) attained by economically acceptable amounts of hydrolase; (2) industrially competitive throughput ([substrate] ≥ 2 M); and (3) facile separation between a digested product and an unaffected substrate. This paper will then deal with illustrative case studies threefold each in which all the above-mentioned requirements have been met successfully: (1) (*R*)-selective hydrolysis of ethyl (±)-tetrahydrofuran-2-carboxylate (2.0 M) by an *Aspergillus melleus* protease in a 1.5 M phosphate buffer (pH 8.0) at 10 °C with $E = 60$ and isolation of (*R*)-tetrahydrofuran-2-carboxylic acid of 99.1% ee, a building block for furopenem (a β-lactam antibiotic), as its crystalline salt with dicyclohexylamine in 22% overall yield;[1] (2) (*R*)-selective hydrolysis of methyl (±)-5,5-dimethyl-1,3-thiazolidine-4-carboxylate (3.0 M) by a thermally stable *Klebsiella oxytoca* hydrolase (produced in quantity by engineered *E. coli*) at 60 °C with $E = 245$ and conversion of the digested acid into (*R*)-3-*tert*-butoxycarbonyl-5,5-dimethyl-1,3-thiazolidine-4-carboxylic acid of 99.4% ee, an intermediate for JE-2147 (an HIV protease inhibitor) in 24% overall yield by treatment with $(Boc)_2O$ after extractive removal of the unaffected (S)-ester at pH 11.5;[2] and (3) (*R*)-selective hydrolysis of (±)-1-benzyloxy-3-chloropropan-2-yl hydrogen succinate (2.0 M) by a *Serratia marcescens* esterase in a 0.3 M phosphate buffer (pH 7.0) at 25 °C and conversion of the unaffected (*S*)-ester into (*S*)-*O*-benzylglycidol of > 98% ee, a versatile chiral building block, in 40% overall yield by treatment with NaOH (5.0 equiv) after extractive removal of the digested alcohol at pH 9.[3]

(1) M. Ikunaka, *chimica oggi/Chemistry Today* **2005**, *23*, 58. (2) M. Ikunaka, *Catalysis Today* **2004**, *96*, 93. (3) M. Ikunaka, *et al*., *Org. Process Res. Dev.* **2003**, *7*, 289.