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Resolution of 1-(2-Naphthyl)ethanol by a Combination of an Enzyme-Catalyzed Kinetic Resolution with a Fluorous Triphasic Separative Reaction

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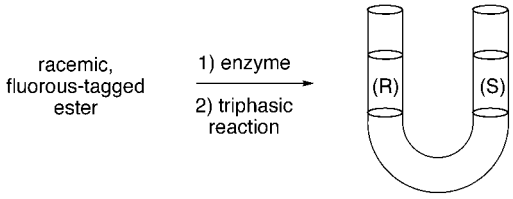
ABSTRACT



Kinetic resolution of a fluorous ester *rac*-1 with *Candida antarctica* B lipase provided a mixture of enantioenriched alcohol (*R*)-2 and fluorous ester (*S*)-1. The mixture was subjected to a fluorous triphasic reaction to give both enantiomers of 1-(2-naphthyl)ethanol 2 in high ee without chromatographic separation or fluorous–organic liquid–liquid extractive purification.

Kinetic resolutions of racemates are often the cheapest and most practical routes to enantiopure compounds, especially when both enantiomers are desired.[1] These resolutions typically require at least three steps: (1) stereoselective conversion of one of the enantiomers into a new chemical product, (2) separation of the starting compound (ideally now one enantiomer) from the new product (ideally the other), and (3) conversion of the new product to the starting material (or the reverse, depending on which product is desired). For example, resolution of a racemic mixture of esters of secondary alcohols might involve enzyme-catalyzed enantioselective deacylation, separation of the resulting alcohol from the ester, and deacylation of the remaining ester (or reacylation of the alcohol). As methods for enantioselective reactions continue to improve, the separation step in the process increasingly becomes the bottleneck.

Recently, Theil and co-workers reported the efficient and enantioselective enzyme catalyzed acylation of 1-phenylethanol and several other alcohols with a fluorous acylating agent.[2] Repeated extractions with a fluorous solvent were needed to separate the fluorous ester from the unreacted alcohol, so this was an enantioselective fluorous tagging reaction in need of an efficient separation. At about the same time, Curran and co-workers reported an attractive resolution of fluorous-tagged secondary alcohols by using a fluorous triphasic reaction.[3] But there are no good methods to enantioselectively adorn secondary alcohols with fluorous tags, so this was an efficient separation and detagging process in search of an enantioselective reaction. We report here that the combination of an enantioselective, enzyme-catalyzed

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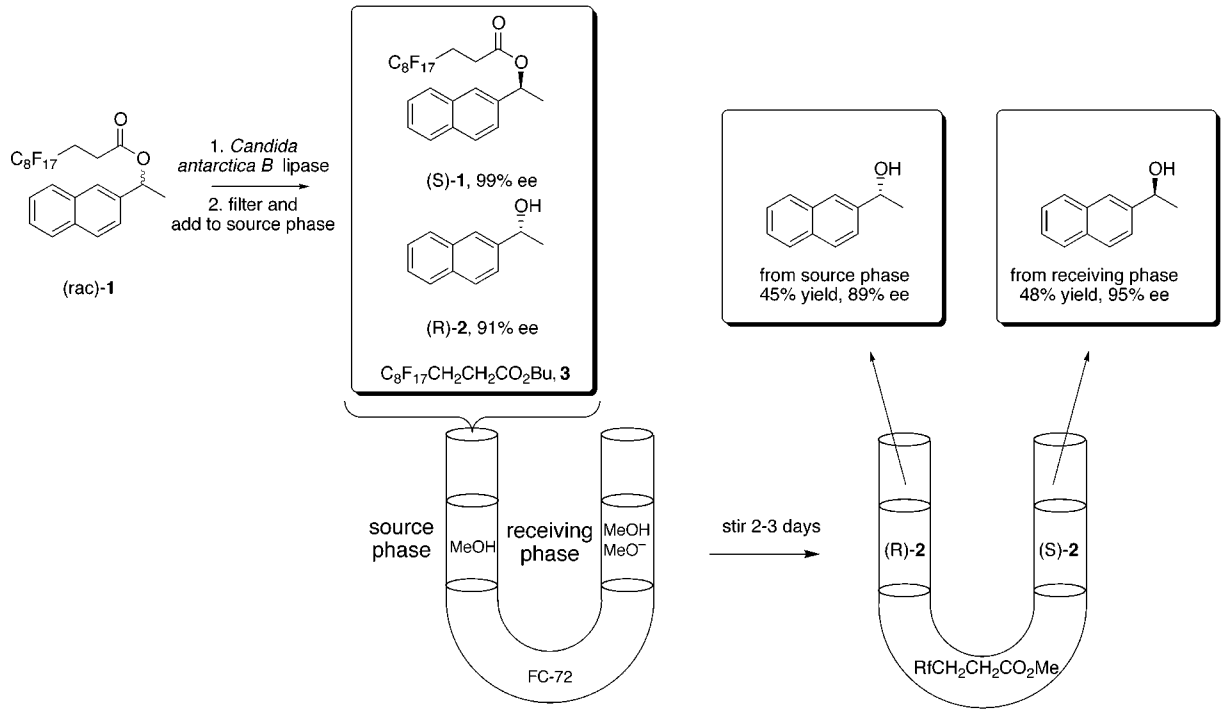

Figure 1. Kinetic resolution by enzymatic deacylation and fluorous triphasic reaction/separation.

reaction with a fluorous triphasic separative reaction of the resulting product mixture indeed results in a practical and efficient kinetic resolution process. The separation and deacylation are combined, so the new process requires only two steps rather than three.

To illustrate the new method, we chose to resolve *rac*-1-(2-naphthyl)ethanol by enantioselective deacylation.[4] Racemic ester **1** was readily prepared by acylation of 1-(2-naphthyl)ethanol with 2*H*,2*H*,3*H*,3*H*-perfluoroundecanoyl chloride.[2,4] The process that resolves *rac*-**1** into (*S*)-**1** and (*R*)-**2** is shown in Figure 1.

The kinetic resolution of fluorous ester *rac*-**1** was conducted with *Candida antarctica* B lipase,[4,5] and the reaction was stopped when the conversion reached about 50%. The lipase was removed by filtration, and the resulting crude mixture containing ester (*S*)-**1** and alcohol (*R*)-**2** was used for the fluorous triphasic reaction. In a control experiment, ester **1** and alcohol **2** were separated by silica gel column chromatography to give (*R*)-**2** in 50% yield with >99% ee. Saponification of ester (*S*)-**1** with NaOMe gave alcohol (*S*)-**2** in 50% yield with 91% ee.

In a typical triphasic experiment,[3,6] a U-tube was charged with FC-72 (perfluorohexanes), and the mixture obtained from the kinetic resolution was added to the source phase (MeOH/$CHCl_3$). A solution of NaOMe/MeOH made up the receiving phase. All three phases were gently stirred at room temperature for 3 days. Evaporation of the source phase gave alcohol (*R*)-**2** with 89% ± 1% ee. Workup of the receiving phase provided (*S*)-**2** with 95% ± 2% ee. The yields of (*R*)-**2** and (*S*)-**2** were comparable to those obtained from silica gel column chromatography followed by saponification (45% and 48%, respectively). Methyl (3-perfluorooctyl)propionate was isolated from the FC-72 phase.[7]

The ee of each enantiomer of the alcohol isolated from the triphasic reaction was marginally lower (2−4%) than the corresponding reference product. In an effort to identify how

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(5) **Kinetic Resolution of *rac*-1.** A solution of the racemic ester *rac*-**1** (5 mmol) in acetonitrile (120 mL) was treated with *n*-butanol (20 mmol) and *C. antarctica* B lipase (Chirazyme L-2, c.-f., lyo. from Roche Diagnostics, Mannheim) (8.0 g). The reaction mixture was stirred at ambient temperature until the conversion reached ca. 50% (estimated by TLC, 7 days). The lipase was removed by filtration and washed with acetone (2 × 40 mL). The combined filtrates were evaporated under reduced pressure to provide a mixture of ester (*S*)-**1**, alcohol (*R*)-**2**, and butyl ester **3** (butyl 2*H*,2*H*,3*H*,3*H*-perfluoroundecanoate). An aliquot of this mixture (116 mg) was purified by silica gel column chromatography (15−30% EtOAc/hexane) to give alcohol (*R*)-**2** (16.0 mg, 50% yield, >99% ee) and ester (*S*)-**1** (60 mg). Treatment of (*S*)-**1** with NaOMe/MeOH at room temperature for 30 min to give (*S*)-**2** (15 mg, 50% yield, 91% ee). The ee's of (*S*)-**2** and (*R*)-**2** were determined by chiral HPLC (column: Chiralcel OJ, eluent: *n*-hexane/2-propanol (9:1), flow rate: 1 mL/min, UV detection at 254 nm).

(6) **Fluorous Triphasic Reactions.** To an U-shape tube charged with FC-72 (15 mL) was added a solution of the mixture of ester (*S*)-**1**, alcohol (*R*)-**2**, and butyl ester **3** (116 mg) in MeOH/$CHCl_3$ (6 mL, 5:1) to the substrate side and NaOMe (0.2 mL, 25wt % in MeOH) in MeOH (6 mL) to the reagent side. All three phases are gently stirred at room temperature for 72 h. The source phase was taken up with a pipet and evaporated to dryness. The residue was passed through a silica plug with 25% EtOAc/hexanes to give (*R*)-**2** (13 mg, 45% yield, 95 ± 1% ee). The receiving phase was taken up and added to 1 N aqueous HCl. After extraction with diethyl ether, the ether layer was dried over magnesium sulfate and evaporated to dryness. The residue was passed through a silica plug with 25% EtOAc/hexanes to give (*S*)-**2** (14 mg, 48% yield, 89 ± 2% ee). The % ee was determined by chiral HPLC as mentioned above and was reported as an average of the results from two triphasic reaction experiments.

(7) Due to its poor solubility in organic solvents, the recovery of methyl (3-perfluorooctyl)propionate is moderate (about 50%) in these small-scale experiments.

this erosion occurs, several control experiments were conducted. A sample of racemic 1-(2-naphthyl)ethanol was subjected to the same conditions as in Figure 1; however, nothing was found in the NaOMe/MeOH receiving phase. In contrast, when acetonitrile was used in place of methanol as the source and receiving phases, a small amount (~4%) of the alcohol was transported through the fluorous phase over the course of 3 days.[3] We next repeated the triphasic reaction by adding (*S*)-**1** and (*R*)-**2** to the source phase but omitting NaOMe from the receiving phase. Only fluorous ester (*S*)-**1** was found in the receiving phase; alcohol (*R*)-**2** could not be detected. These experiments do not provide a convincing explanation for the loss of ee, but we decided that the loss was too small to merit additional study.

To summarize, we have demonstrated for the first time the utility of a fluorous triphasic reaction coupled with an enzyme-catalyzed kinetic resolution of a racemic ester. An enzyme-catalyzed deacylation reaction of a racemic fluorous ester stereoselectively provides a mixture of the detagged alcohol and the fluorous ester. Separation of the alcohol from the ester and saponification of the ester are carried out simultaneously in a triphasic process instead of sequentially. The fluorous tag allows the ester to pass from one side to the other, but back passage is blocked by tag removal. In the end, the source side contains one enantiomer, the receiving side contains the other enantiomer, and the residual tag is in the middle. Time-consuming, solvent-intensive, extractive or chromatographic separations are bypassed. This example serves as a model for a new class of resolutions that couple enzymatic (or chemical) addition or removal of a fluorous tag with subsequent triphasic separation and reaction.

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