DOUBLE PARALLEL DYNAMIC RESOLUTION THROUGH LIPASE-CATALYZED ASYMMETRIC TRANSFORMATION

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**General methods**

Reagents were obtained from commercial suppliers and used as received. Lipase PS “Amano” IM (EC 3.1.1.3) was purchased from Amano Enzyme Inc. $^1$H and $^{13}$C NMR data were recorded on a Bruker Avance 400 (100 MHz) and/or a Bruker Avance 500 (125 MHz), respectively. Chemical shifts are reported as $\delta$ values (ppm) with CDCl$_3$ ($^1$H NMR $\delta$7.26, $^{13}$C NMR $\delta$77.0) as an internal standard. $J$ values are given in Hertz (Hz). Analytical high performance liquid chromatography (HPLC) with chiral stationary phase was performed on an HP-Agilent 1110 Series controller and a UV detector, using a Daicel Chiralpak OJ column (4.6 × 250 mm, 10 µm). Solvents for HPLC use were of spectrometric grade. Thin layer chromatography (TLC) was performed on precoated Polygram® SIL G/UV 254 silica plates (0.20 mm, Macherey-Nagel), visualized with UV-detection. Flash column chromatography was performed on silica gel 60, 0.040-0.063 mm (SDS).

**Generation of dynamic systems and lipase-catalyzed asymmetric transformation**

The dynamic systems were generated by adding 1 equiv of each aldehyde (1, 2 and 3, 0.1 mmol), together with 1 equiv of 2-nitropropane A (0.1 mmol), 1-butanethiol B (0.1 mmol) and TEA (0.5 mmol) in the specific dry solvent (0.6 mL). After addition of phenyl acetate (3 equiv, 0.3 mmol), the solution was transferred to a 1.5 mL sealed-cap vial containing PS-IM and ground 4 Å molecular sieves (20 mg), dried for 2 days before use, under argon atmosphere at RT or 0 °C. $^1$H NMR was used to follow the reaction process until completion. For complex systems, work-up and column purification were necessary before chiral analysis. The reaction mixture was filtered to remove PS-IM, and the solvent removed by evaporation. The crude product was dissolved in CH$_2$Cl$_2$, and the solution was extracted with water and brine. Drying over MgSO$_4$, filtration and evaporation provided a yellow oil, which was purified by flash column chromatography using hexanes/EtOAc (25:1, v/v) as eluent. For similar systems but with only one aldehyde as starting material, the crude reaction mixtures were directly sampled and analyzed by $^1$H NMR and HPLC.

**Synthesis of racemic compound 4B**

3-nitrobenzaldehyde 1 (30.2 mg, 0.2 mmol) was dissolved in CH$_2$Cl$_2$ (0.6 mL), after which 1-butanethiol (21.6 µL, 0.24 mmol), TEA (83.4 µL, 0.6 mmol) and acetic anhydride (56.7 µL, 0.6 mmol) were added to the solution. The reaction mixture was stirred at RT for 2 d. After neutralization with 1M HCl solution, the reaction solution was extracted with CH$_2$Cl$_2$ (2 mL × 3), dried over MgSO$_4$, filtered, and the solvent evaporated under vacuum. The crude product was further purified using column chromatography (hexane/EtOAc, 10:1 (v/v)) providing compound 4B (10.6 mg) as a light yellow oil. $^1$H NMR (500 MHz, CDCl$_3$, 25 °C) $\delta$ 0.90 (t, $J$=7.4, H, CH$_3$), 1.39 (m, 2H, CH$_2$), 1.59 (m, 2H, CH$_2$), 2.20 (s, 3H, CH$_3$), 2.54 (m, 1H, CH$_2$), 2.71 (m, 1H, CH$_2$), 7.03 (s, 1H, CH), 7.55 (t, $J$=7.9, 1H, CH), 7.77 (d, $J$=7.9, 1H, CH), 8.18 (d, $J$=7.9, 1H, CH), 8.30 (s, 1H, CH); $^{13}$C NMR (125 MHz, CDCl$_3$, 25 °C) $\delta$ 13.7, 21.3, 22.0, 31.0, 31.7, 78.2, 121.5, 123.5, 129.7, 132.5, 140.4, 148.5, 169.9.
$^1$H NMR-, $^{13}$C NMR-spectra of product 4B
HPLC analyses
The enantiomeric purity of product 4B from the dynamic systems was determined by analytical HPLC using a Daicel Chiralpak OJ column. Analyses were carried out at 298 K and 210 nm for 40 min, using hexane:iPrOH (90:10, v/v) as mobile phase.

a) Racemic mixture of 4B.

b) Product 4B separated from dynamic system.