Supporting Information
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Continuous-Flow Kinetic Resolution of (±)-cis-1-Amino-2-Indanol by Lipase-Catalyzed N-Acetylation

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Supporting Information

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1. Experimental

1.1 General

Novozyme 435® was purchased from Aldrich (≥5,000 U/g). All the other chemicals were purchased from Aldrich or TCI. Continuous flow reactions were performed by FRX (Syrris) equipped with an enzyme-filled solvent plus column (Ommifit, 15 mm ID, length adjustable). NMR spectra were recorded on an Agilent 400 MHz spectrometer using CDCl₃ as the solvent. FT-IR spectra were registered with an Agilent FTIR Cary 630 infrared spectrophotometer. HR-MS were measured with electrospray ionization (ESI) and a Q-TOF mass analyzer. Chiral HPLC was performed using an 1260 Series HPLC (Agilent) with a SPD-M10A UV detector and CHIRALCEL OJ-H 4.6*250 mm (operating temperature: 25 °C; detection: absorbance at 254 nm; injection volume: 10 ml; mobile phase: n-hexane (0.2% TFA) and i-PrOH (90 : 10, flow: 0.5 ml/min). TLC was carried out on Kieselgel 60F254 (Merck) sheets.

1.2 (1S,2R)-1-Acetamido-2-indanol (2)

White solid; IR (neat, cm⁻¹): 3444, 3299, 1539; ¹H NMR (400 MHz, CDCl₃) δ 7.22 (s, 4H), 6.23 (d, J = 7.2 Hz, NH), 5.32 (dd, J = 8.2, 5.1 Hz, 1H), 4.57 (td, J = 5.1, 2.3 Hz, 1H), 3.13 (dd, J =16.5, 5.3 Hz, 1H), 291 (dd, J = 16.5, 2.1 Hz, 1H), 2.57 (br-s, 1H), 2.07 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): 170.9, 140.6, 139.9, 128.2, 127.2, 125.3, 124.5, 73.5, 57.6, 39.6, 23.3; HR-MS (ESI): m/z 192.1016 [M+H]+ (calcd for C₁₁H₁₄NO₂+ 192.1019); [α]20/D +11.7 (c = 0.25, CHCl₃).

1.3 General procedure for the screening of acyl donors.

To a separate small vials containing 0.2 M solutions of (±)-cis-1-amino-2-indanol (298 mg, 2.0 mmol) in THF, different acyl donors (1.1 eq) in THF (0.5 ml) or 0.5 ml of acyl donor (50 eq) was added. Novozyme 435® (20 mg) was added to each vial in one portion, and the turbid solutions were shaken (125 rpm) at 30 °C. After 6 h and 24 h, the enzyme was filtered off from the samples and the solutions were dried in-vacuo. For HPLC analysis, samples were diluted with 1.5 ml of THF and EtOH (2 : 1).

1.4 General procedure for the screening of solvents.

To a separate small vials containing 0.2 M solutions of (±)-cis-1-amino-2-indanol (298 mg, 2.0 mmol) in different solvents, 0.5 ml of ethyl acetate (50 eq) was added. Novozyme 435® (20 mg)
was added to each vial in one portion, and the turbid solutions were shaken (125 rpm) at 30 °C. After 6 h and 24 h, the enzyme was filtered off from the samples and the solutions were dried in-vacuo. For HPLC analysis, samples were diluted with 1.5 ml of THF and EtOH (2 : 1).

1.5 General Procedure for the flask reaction
To a separate small vials containing 0.2 M solutions of (±)-cis-1-amino-2-indanol (298 mg, 2.0 mmol) in THF, 0.5 ml of ethyl acetate (50 eq). Novozyme 435® (20 mg) was added to each vial in one portion, and the turbid solutions were shaken (125 rpm) at 30 °C. After 6 h, 12 h, 24 h, and 48 h, the enzyme was filtered off from the samples. For HPLC analysis, samples were diluted with 0.5 ml of EtOH.

1.6 General Procedure for the continuous flow reaction
Novozyme 435® (2.0 g) was packed into a glass column with an aluminum heating jacket for maintaining temperature at 30 °C. The column was fully washed with THF and then fed with a solution of (±)-cis-1-amino-2-indanol (0.1 M) in ethyl acetate and THF (1:1). At various flow rates (2.0, 1.0, 0.5, 0.25, and 0.1 ml/min), 1 ml of samples were collected. For HPLC analysis, samples were diluted with 0.5 ml of EtOH.
2. Chromatograms

2.1. Standard compounds

2.1.1 (±)-cis-1-amino-2-indanol
2.1.2. (1R,2S)-1-Acetamido-2-indanol

2.1.3. (1S,2R)-1-Acetamido-2-indanol
2.2 Enantiomer selective $N$-acetylation of (±)-$cis$-1-amino-2-indanol by Novozyme 435 with ethyl acetate in different solvents

2.2.1. MTBE: tert-butyl methyl ether

![MTBE chromatogram](image)

2.2.2. THF

![THF chromatogram](image)
2.2.3 CH₂Cl₂

(+)-cis-aminindanol

(+)-(1R,2S)-1

2.2.4 Toluene

(+)-cis-aminindanol

(+)-(1R,2S)-1

Toluene
2.3. Enantiomer selective N-acetylation of (±)-cis-1-amino-2-indanol by Novozyme 435 with n-butyl acetate in THF

2.3.1. n-Butyl acetate (1.0 equivalent) 6h

2.3.2. n-Butyl acetate (1.0 equivalent) 12h
2.3.3. *n*-Butyl acetate (1.0 equivalent)_24h

2.3.4. *n*-Butyl acetate (50 equivalent)_6h
2.3.5. \( \alpha \)-Butyl acetate (50 equivalent)_12h

2.3.6. \( \alpha \)-Butyl acetate (50 equivalent)_24h
2.4. Enantiomer selective N-acetylation of (±)-cis-1-amino-2-indanol in flask mode

2.4.1. Ethyl acetate (1.0 equivalent) \_6h

2.4.2. Ethyl acetate (1.0 equivalent) \_12h
2.4.3 Ethyl acetate (1.0 equivalent) 24h

2.4.4 Ethyl acetate (1.0 equivalent) 48h
2.4.5. Ethyl acetate (50 equivalent)_6h

2.4.6 Ethyl acetate (50 equivalent)_12h
2.4.7. Ethyl acetate (50 equivalent) 24h

2.4.8. Ethyl acetate (50 equivalent) 48h
2.5. Enantiomer selective N-acetylation of (±)-cis-1-amino-2-indanol in microflow system

2.5.1. Flow rate 2ml/min

2.5.2. Flow rate 1ml/min
2.5.3. Flow rate 0.5ml/min

2.5.4. Flow rate 0.25ml/min
2.5.5. Flow rate 0.1ml/min
3. NMR spectrum

3.1.1. (1S, 2R) N-(2-hydroxy-2, 3-dihydro-1H-inden-1-yl)acetamide

$^1$H NMR (400MHz, CDCl$_3$)

$^{13}$C NMR (400MHz, CDCl$_3$)