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Supporting Information

Dynamic Kinetic Resolution of a Tertiary Alcohol

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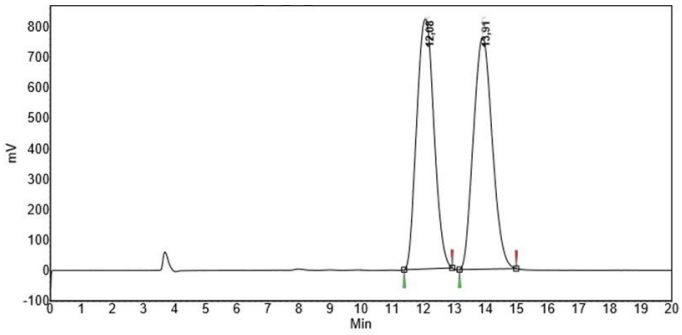
Content

1. Experimental Procedures

^{1}H-NMR spectra were recorded in $CDCl_3$ or C_6D_6 on a *Bruker* FT-NMR-spectrometer Avance III 500. The chemical shifts are given in ppm and the coupling constant *J* is given in MHz. High performance liquid chromatography was done with a LC2000SFC-HPLC system from *Jasco* (pumps PU-2080plus, automatic back pressure regulator BP-2080plus, column thermostat CO-2060plus, multiwavelenght detector MD-2010plus and autosampler AS-2059plus). The samples were separated with Chiralpak® columns from *Daicel*. The chromatograms were evaluated with the software Galaxy Chromatography Data. Column chromatography was performed with a *Biotage* Isolera 1 flash purification system. TLC was performed on VWR 0.2 mm Silica Gel 60 F_{254} aluminium sheets. The reactions were done in a ChemiStation PPM-5512 from *EyelaWorld*. CAL-A (Lipase A, *Candida antarctica*, immobilized on immobead 150, ≥ 500 U/g) and PhosphonicS^{TM} POVO were purchased from *Sigma Aldrich*. The V-MPS4 catalyst (0.25 mmol/g) and the $O{=}V(OSiPh_3)_3$ catalyst were prepared according to literature.[1,2]

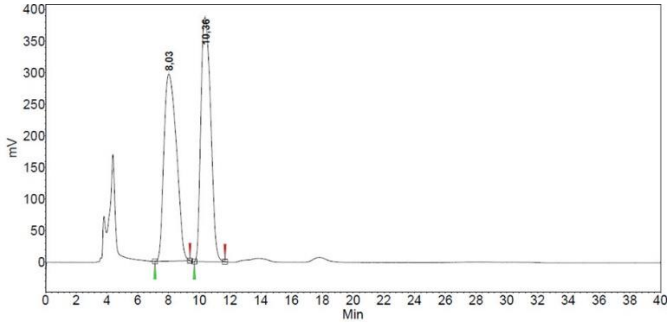
1.1 Synthesis of 1,2,3,4-tetrahydronaphthalene-1-ol (*rac*-1)

The synthesis was performed under argon atmosphere. Methyl lithium (12.8 mL, 1.6 Min Et_2O, 1.50 eq.) was added dropwise to a solution of *α*-tetralone (1.82 mL, 1.00 eq.) in dry diethyl ether (136 mL) under ice bath cooling. The solution was allowed to warm to room temperature and stirred for three hours. The solution was then heated to reflux for 30 minutes. Afterwards it was cooled to 0 °C and saturated aqueous NH_4Cl-solution (20 mL) and water (15 mL) were added. After phase separation the aqueous media was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure. Alcohol *rac*-**1** was obtained as a colourless solid (1.15 g, 51 %). Structural analysis was done by ^{1}H-NMR.[3] HPLC (*Daicel* AD-H (4.6 mm ID x 250 mm), *n*-hexane/2-propanol 97.5:2.5 flow rate 1.0 mL/min, λ = 210 nm, R_{t1} = 12.1 min, R_{t2} = 13.9 min).



1.2 Synthesis of 1,2,3,4-tetrahydronaphthalene1-yl-acetate (*rac*-2)

To a solution of alcohol *rac*-**1** (184 mg, 1.13 mmol) in dichloromethane (11.3 mL), acetic anhydride (1.07 mL, 11.3 mmol), DMAP (42.2 mg, 339 µmol) and pyridine (274 µL, 3.39 mmol) were added. The solution was heated to 35 °C and stirred for 18 hours. Saturated aqueous NH_4Cl-solution (2 mL) and water (5 mL) were added. After phase separation the aqueous media was extracted with dichloromethane (3 x10 mL). The combined organic layers were dried over magnesium sulphate and the solvent was removed under reduced pressure. Acetate *rac*-**2** was obtained as a colourless oil (103 mg, 45 %). Structural analysis was done by ^{1}H-NMR.[3] HPLC (*Daice*l OD-H (4.6 mm ID x 250 mm), *n*-hexane/2-propanol 99.5:0.5 flow rate 1.0 mL/min, λ = 210 nm, R_{t1} = 8.00 min, R_{t2} = 10.4 min).



1.3 Stability test of the CAL-A

To a solution of the alcohol *rac*-**1** (8.60 mg, 53.0 µmol) in vinyl acetate (663 µL) was added fresh CAL-A (25.8 mg, 3 w/w). The suspension was stirred for 24 hours at 25 °C and 800 rpm. The CAL-A enzyme preparation was filtered off and a fresh solution of substrate *rac*-**1** (10.3 mg, 63.5 µmol) in vinyl acetate (791 µL) was added. After stirring for 24 hours at 25 °C and 800 rpm, the CAL-A was again filtered off and a fresh solution of substrate *rac*-**1** (8.15 mg, 50.2 µmol) in vinyl acetate (628 µL) was added. Suspension was stirred for 24 hours at 25 °C and 800 rpm for the last time.

Table 1: Stability test of the CAL-A enzyme preparation with the yield of the formed acetate, the optical purities of remaining alcohol and formed acetate and the calculated E-value.

Entry	Accumulated Reaction time (h)	Yield of acetate (*R*)-**2** (%)	Optical purity (*S*)-**1** (%)	Optical purity (*R*)-**2** (%)	E-value
1	24	37	58	>99	>200
2	48	22	30	>99	>200
3	72	18	19	>99	>200

1.4 Standard procedure for the oxovanadium-catalyzed racemization of tertiary alcohol (*S*)-1:

The enantiomerically enriched tertiary alcohol (*S*)-**1** (44% *ee*, 1 eq.) was placed under argon and treated with different oxovanadium-catalysts (1 mol%) in various solvents (0.08 M) and the suspension was shaken at different temperatures for 24 hours. Afterwards the immobilisate was filtered off and the solvent was removed in vacuo. A crude product was analyzed by ^{1}H-NMR-spectroscopy and HPLC-chromatography. HPLC (*Daicel* AD-H (4.6 mm ID x 250 mm), *n*-hexane/2-propanol 97.5:2.5 flow rate 1.0 mL/min, λ = 210 nm, (*S*)-**1** = 12.1 min, (*R*)-**1** = 13.9 min).

1.5 Standard procedure for the kinetic resolution of the tertiary alcohol *rac*-1

The racemic alcohol *rac*-**1** and the lipase CAL-A (1 w/w) were placed in an Eppendorf tube to which were added different solvents (0.08 M) and freshly distilled vinyl acetate (10 eq.). The suspension was shaken at 25 °C and 1200 rpm for 48 hours. Afterwards the immobilisate was filtered off and the solvent was removed in vacuo. A crude product was analyzed by ^{1}H-NMR-spectroscopy and HPLC-chromatography. HPLC (Daicel AD-H, *n*-hexane/2-propanol 97.5:2.5 flow rate 1.0 mL/min, λ = 210 nm, (*S*)-**1** = 12.1 min, (*R*)-**2** = 13.9 min). HPLC (*Daicel* OD-H (4.6 mm ID x 250 mm), *n*-hexane/2-propanol 99.5:0.5 flow rate 1.0 mL/min, λ = 210 nm, (*R*)-**2** = 8.00 min, (*S*)-**2** = 10.4 min).

1.6 Dynamic kinetic resolution process of tertiary alcohol *rac*-1

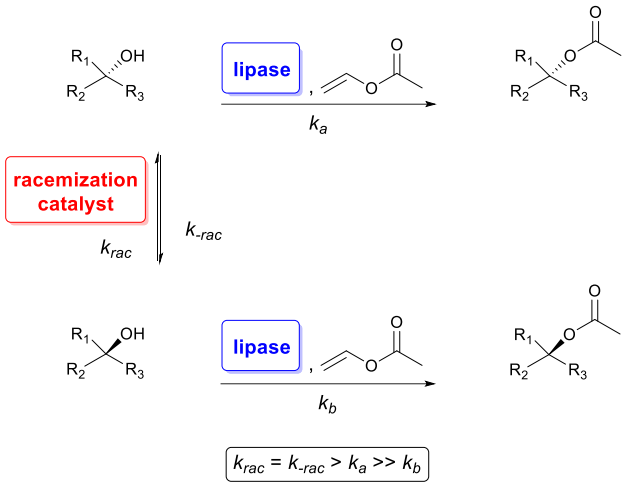
Tertiary alcohol *rac*-**1** (1 eq.) was placed in a dried Schlenk-tube and dissolved in dry diisopropyl ether (0.08 M). Freshly distilled vinyl acetate (10 eq.), CAL-A (*Candida antarctica,* 1 w/w) and V-MPS4 (1 mol%) were added and the suspension was stirred at 1200 rpm for 72 h in a *ChemiStation*. The immobilisates were filtered off and the solvent was removed, Crude product was analyzed by ^{1}H-NMR-spectroscopy and HPLC-chromatography. HPLC (*Daicel* AD-H, *n*-hexane/2-propanol 97.5:2.5 flow rate 1.0 mL/min, λ = 210 nm, (*S*)-**1** = 12.1 min, (*R*)-**1** = 13.9 min). HPLC (Daicel OD-H, *n*-hexane/2-propanol 99.5:0.5 flow rate 1.0 mL/min, λ = 210 nm, (*R*)-**2** = 8.00 min, (*S*)-**2** = 10.4 min).

1.7 Dynamic kinetic resolution of tertiary alcohol *rac*-1 in a sequential batch process

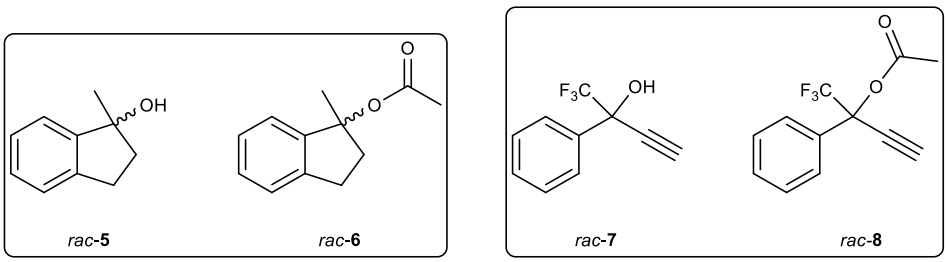
Tertiary alcohol *rac*-**1** (49.8 mg, 307 µmol, 1.00 eq.) was placed in a heated Schlenk-tube and dissolved in dry diisopropyl ether (3.60 mL, 0.08 M). Vinyl acetate (285 µL, 10.0 eq.) and lipase CAL-A (*Candida antarctica*, 25.8 mg, 0.5 w/w) were added. The suspension was stirred at 25 °C and 1200 rpm for 48 h in a ChemiStation. Additional CAL-A (28.4 mg, 0.5 w/w) and vanadium catalyst V-MPS4 (12.0 mg, 3.00 µmol, 1 mol%) were added and stirred for further 24 h. Next, CAL-A (102 mg, 2 w/w) was added and the suspension was stirred for 72 h at 25 °C and 1200 rpm. The immobilisates were filtered off and the solvent was removed under vacuum. The resulting reaction mixture was again treated with vinyl acetate (285 µL, 10.0 eq.) and CAL-A (24.3 mg. 0.5 w/w) in diisopropyl ether (3.6 mL, 0.08 M). The suspension was stirred at 25 °C and 1200 rpm for 48 h in a *ChemiStation*. Further CAL-A (24.4 mg, 0.5 w/w) and V-MPS4 (12.5 mg, 3.13 µmol, 1 mol%) were added and stirred for another 24 h. The resulting suspension was treated with CAL-A (76.2 mg, w/w) and V-MPS4 (12.4 mg, 3.10 µmol, 1 mol%) again and stirred for 72 h. The immobilisates were filtered off and the solvent was removed under vacuum. The crude product was analyzed by ^{1}H-NMR-spectroscopy and HPLC-chromatography to find that (*R*)-**2** (77% NMR yield, >99% ee) was obtained along with the recovery of **1** (23 % NMR yield, 66% *ee*). The formation of **3** and **4** was not observed. HPLC (*Daicel* AD-H, *n*-hexane/2-propanol 97.5:2.5 flow rate 1.0 mL/min, λ = 210 nm, (*S*)-**1** = 12.1 min, (*R*)-**1** = 13.9 min). HPLC (*Daicel* OD-H, *n*-hexane/2-propanol 99.5:0.5 flow rate 1.0 mL/min, λ = 210 nm, (*R*)-**2** = 8.00 min, (*S*)-**2** = 10.4 min).

1.8 Preliminary studies in expanding the substrate scope

Overview about the DKR with further substrates –planned syntheses



Examples of further substrates



Several difficulties could be identified for the various substrates. Partly the problem was the stability of the alcohol and the corresponding acetate (see chapter 1.8.1 and 1.8.2). In addition, there were problems with kinetic resolution (see chapter 1.8.2 part 1 and 2), because it only works in the hydrolysis direction and not in the acetylation direction. In some cases, also the racemization reaction was a problem, because the racemization catalyst did not accept the substrates (see chapter 1.8.3 part 3).

1.8.1 Synthesis of *rac*-1-methylindanol (*rac*-5)

Methyllithium (1.6 M in Et_2O, 100 mL, 160 mmol, 2.30 eq.) was placed in a Schlenk-flask. After cooling down to 0 °C 1-indanone (9.25 g, 70.0 mmol, 1.00 eq.), dissolved in dry diethyl ether (50 mL), was added under ice-bath cooling. After heating up to room temperature, the reaction mixture was stirred for three days. Water (200 mL) was added and an extraction with diethyl ether (3 x 100 mL) followed. The combined organic layers were washed with sat. aq. sodium hydrogen carbonate (200 mL) and water (2 x 200 mL). The organic layers were dried over sodium sulfate and the solvent was removed. Column chromatography (cyclohexane/ethyl acetate 8:1) delivered the pure product (3.94 g, 38 %). Structural analysis was done by ^{1}H-NMR in chloroform-d.
HPLC (*Daicel* OD-H (4.6 mm ID x 250 mm), CO_2/2-propanol 98:2 flow rate 1.0 mL/min, λ = 210 nm, R_{t1} = 25.1 min, R_{t2}= 29.3 min).

1.8.2 Conversion of *rac*-1-methylindanol (*rac*-5) with acetic anhydride

Tetrahydrofurane (15 mL) was placed in a three-neck-flask and treated with *n*-buthyllithium (1.6 M in *n*-hexane, 1.30 mL, 2.08 mmol, 1.50 eq.). *Rac*-**5** (209 mg, 1.41 mmol, 1.00 eq.) was dissolved in tetrahydrofurane (7 mL). This solution was slowly dropped to the *n*-buthyllithium solution at - 40 °C. After warming up to room temperature, acetic anhydride (0.41 g, 4.05 mmol, 2.90 eq.) and tetrabutylammonium iodide (66.0 mg, 0.18 mmol, 0.10 eq.) were added. The reaction mixture was stirred for 32 hours at room temperature and was then refluxed for another one hour. After cooling down to room temperature, a pH-value of 5 was adjusted with hydrochloric acid (2M) and water (20 mL) was added. It was extracted with dichloromethane (3 x 30 mL) and washed with water (20 mL) and sat. aq. sodium hydrogen carbonate solution (2 x 30 mL). The crude product was delivered after drying over sodium sulfate and removing the solvent. Structural analysis was done by ^{1}H-NMR and the expected product could be observed in the crude product.
A column chromatography was performed, but the pure product could not be recovered for stability reasons.

The stability of substrate *rac*-**5** and product *rac*-**6** is a great difficulty in this case. The formation of the elimination products could be observed. Even slightly acidic solvents, such as chloroform, as an NMR solvent, are sufficient to decompose alcohol *rac*-**5** into the elimination products.

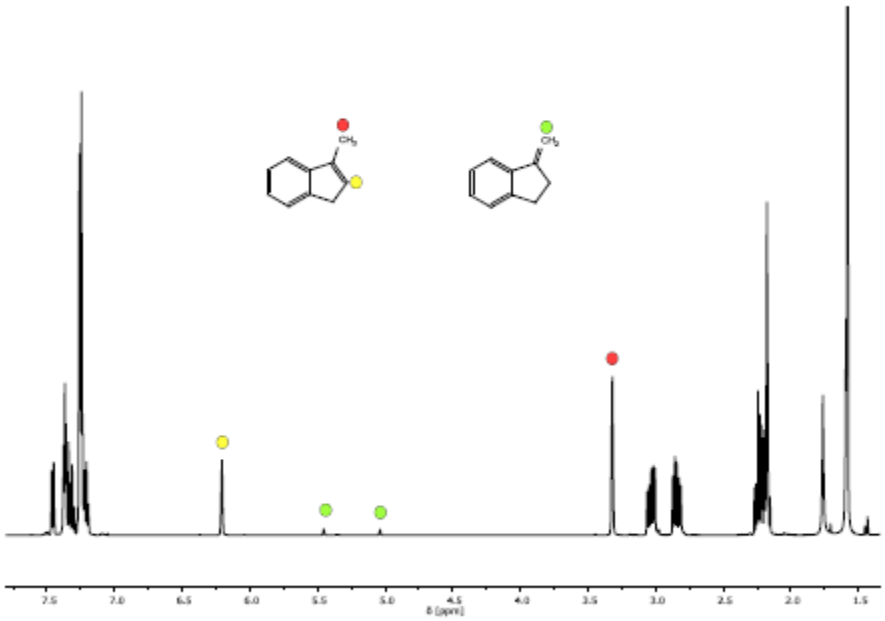


Figure S1. ^{1}H-NMR spectra of the stability test of substrate *rac*-**5** in chloroform-d after a reaction time of five days.

1.8.3 Synthesis of *rac*-1,1,1-trifluoro-2-phenyl-3-butyn-2-yl acetate (*rac*-8)

Tetrahydrofurane (10 mL) was placed in a three-neck-flask and r*ac*-**7** (200 mg, 1.00 mmol, 1.00 eq.) was added. Then, *n*-buthyllithium (1.6 M in hexane, 0.94 ml, 1.50 mmol, 1.50 eq.) was added under ice bath cooling. The reaction mixture was stirred for 15 minutes, followed by the addition of acetyl chloride (214 µL, 3.00 mmol, 3.00 eq.). It was refluxed for one hour. Water (10 mL) was added and it was extracted with diethyl ether (4 x 15 mL). The combined organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (cyclohexane/ethyl acetate 10:1) and the pure product *rac*-**8** (201 mg, 83 %) was delivered. Structural analysis was done by ^{1}H-NMR.[3]

1. Kinetic resolution of *rac*-**8** via hydrolysis

   Rac-**8** (201 mg, 0.83 mmol, 1.00 eq.) was dissolved in a phosphate buffer (30 mL, pH =7), followed by the addition of CAL-A (217 mg, 1.00 w/w). The reaction mixture was stirred for 48 hours at 25 °C. The immobilisate was filtered off and the aqueous phase was extracted with dichloromethane (3 x 20 mL). The solvent was removed after drying over sodium sulfate and the crude product was purified by column chromatography (cyclohexane/ethyl acetate 10:1). A pure product (*S*)-**7** (23%, 92% *ee*) was obtained.

2. Standard procedure for the kinetic resolution of *rac*-**7** *via* acetylation

   Rac-**7** (5 mM) was dissolved in various organic solvents and treated with vinyl acetate (200 mM). CAL-A was added and the mixture was stirred at different reaction temperatures for six days. The immobilisate was filtered off and the solvent was removed.
   In this case, no conversion to the expected product **8** was observed, independent of the solvent, the amount of lipase or the reaction temperature.

3. Racemization of (*S*)-**7**
   (*S*)-**7** (8.70 mg, 40.0 µmol, 1.00 eq.) was dissolved in isooctane (5 mL). Then, tris(triphenylsilyloxy)oxovanadium (20.5 mg, 20.0 µmol, 53 mol%) was added and it was stirred at room temperature. Racemization was monitored *via* GC. After 52 hours reaction time, the mixture was heated up to 50 °C and after another 24 hours reaction time, it was refluxed. No racemization was observed, independent of the reaction time or reaction temperature.

2. NMR of crude product in the sequential DKR process

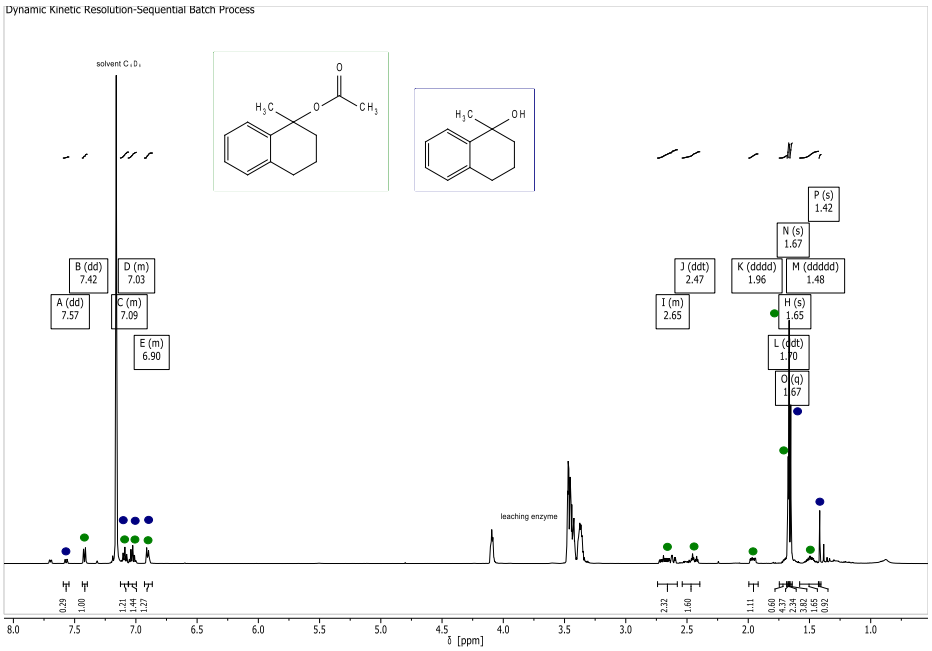


Figure S2. ^{1}H-NMR spectra of the dynamic kinetic resolution of *rac*-**1** in a sequential batch process. Determination of the conversion was based on the integrals of the starting material **1** and the product **2**.

3. References

[1] K. Sugiyama, Y. Oki, S. Kawanishi, K. Kato, T. Ikawa, M. Egi, S. Akai, *Catal. Sci. Technol.*, **2016**, *6*, 5023-5030.

[2] F. Preuss, H. Noichl, *Z. Naturforsch.* **1987**, *42b*, 121-129.

[3] D. Özdemirhan, S. Sezer, Y. Sönmez, *Tetrahedron: Asymmetry*, **2008**, *19*, 2717-2720. D. Özdemirhan, *Synth. Commun.* **2017**, *47*, 629-645.