### En route to multicatalysis: Kinetic resolution of *trans*-cycloalkane-1,2-diols *via* oxidative esterification

#### Christine Hofmann, Sören M. M. Schuler, Raffael C. Wende, and Peter R. Schreiner\*

Institute of Organic Chemistry, Justus-Liebig University, Heinrich-Buff-Ring 58, 35392 Giessen, Germany. Fax: 0641/99 34309; Tel: 0641/99 34300; E-mail: prs@uni-giessen.de

**Supporting Information** 

#### Contents

1. General Remarks	S-2
2. Synthesis of peptide A and C	S-2
3. Availability of the aldehydes and racemic starting materials	S-2
4. Description of the catalytic experiments for the variation of the acids (Table 1)	S-2
5. Identification of mixed anhydrides of propanoic acid and 4-nitrobenzoic acid by NMR	S-3
6. Time-resolved NMR investigations with 2,4,6-trichlorobenzoic acid	S-4
7. Description of the preparative experiments with <i>trans</i> -cycloalkane-1,2-diols (Table 2)	S-10
8. Description of the preparative experiments with <i>trans</i> -cyclohexane-1,2-diol using aldehydes 4b-i (Table 3)	S-15
9. Description of the preparative experiments with multicatalyst C	S-22
10. NMR spectra	S-23
11. Literature	S-30

#### 1. General remarks

Unless otherwise noted, chemicals were purchased from Acros Organics, Alfa Aesar, Aldrich, Lancaster, Merck, Novabiochem or Fluka at the highest purity grade available and were used without further purifications. All solvents were distilled prior to use. Toluene was distilled from appropriate drying agents prior to use and stored under argon atmosphere. The aldehydes were distilled prior to use. All catalytic reactions were carried out under an argon atmosphere employing oven- and flame-dried glassware. Column chromatography and filtration was conducted using Merck silica gel 60 (0.040 - 0.063 mm). TLC R<sub>f</sub> values are reported. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on Bruker AV600, AV400 or AV200 spectrometers, respectively, using TMS as the internal standard with chemical shifts given in ppm relative to TMS or the respective solvent residual peaks. Infrared spectra were recorded on a Bruker IFS25 spectrometer. ESI mass spectra were recorded on a Finnigan LCQDuo spectrometer using methanol solutions of the respective compounds. High resolution ESI mass spectrometry was performed on a Thermo Scientific LTQ FT Ultrahybrid mass spectrometer using methanol solutions of the respective compounds. GC analyses were performed by using Hewlett Packard 5890 and Carlo Erba 2900 gas chromatographs. The analytical HPLC was accomplished by using a Spectra SP 8700 system and the preparative HPLC by using a Knauer system (Knauer Differential-Refractometer, Knauer HPLC Pump 64, Knauer 2151 Variable Wavelength Monitor).

#### 2. Synthesis of peptide A and C

Peptides A and C were synthesized in solution using Boc-strategy and EDC/HOBt mediated couplings as described in the literature. Analytical data of the peptides A and C were identical with those reported in the literature.<sup>[1],[2]</sup>

#### 3. Availability of the aldehydes and racemic starting materials

The achiral aldehydes were purchased and distilled prior to use. Racemic *trans*-cyclopentane-1,2-diol (*rac*-1a) was purchased from Aldrich (97% purity) and used without further purification. Racemic *trans*-cyclohexane-1,2-diol (*rac*-1b) was purchased from Acros Organics (98% purity). *Trans*-cycloheptane-1,2-diol (*rac*-1c) was synthesized according to the method of the *Organikum*<sup>[3]</sup> using freshly distilled cycloheptene (purchased from Aldrich, 92% purity), formic acid, H<sub>2</sub>O<sub>2</sub> followed by a saponification with aq. NaOH. *Trans*cyclooctane-1,2-diol (*rac*-1d) was synthesized via epoxide opening of cyclooctaneoxide (purchased from Alfa Aesar, 99% purity) in water with *p*-toluenesulfonic acid.<sup>[2]</sup>

#### 4. Description of the catalytic experiments for the variation of the acids (Table 1)

#### **Exemplary Description of Standard Conditions for Catalytic Runs provided in Table 1:**

The acids **7a–f** (0.11 mmol) and TEMPO **B** (0.8 mg, 5  $\mu$ mol, 5 mol%) were suspended in 100  $\mu$ L dry toluene. Additionally propanal (7.2  $\mu$ L, 0.10 mmol) and pyridine (8.1  $\mu$ L, 0.10 mmol) were added via an Eppendorf pipette. The reaction mixture was cooled to 0 °C and 1.05 equiv.

of *t*-butyl hypochlorite (0.105 mmol) were then added with an Eppendorf pipette and allowed to stir for 1 h at 0 °C. After completion of the oxidation of aldehyde the reaction was diluted with 20 mL dry toluene and cooled to 0 °C. Catalyst C (3.8 mg, 5  $\mu$ mol, 5 mol%) and *trans*-cyclohexan-1,2-diol (11.6 mg, 0.10 mmol) were added followed by D*i*PEA (17  $\mu$ L, 0.10 mmol). The mixture was stirred for 24 h, quenched with methanol and directly analyzed by chiral GC.

#### Data for diol (rac-1b):



See chapter 7.

#### Data for monopropionate (rac-6b):



See chapter 7.

#### 5. Identification of mixed anhydrides of propionic acid and 4-nitrobenzoic acid by NMR

The mixed anhydrides were prepared by two independent methods as described in the literature.<sup>[4]</sup> The first preparation involved starting from propanal and 4-nitrobezoic acid. In the other method the same anhydride was synthesized by treating propionic acid chloride with 4-nitrobenzoic acid in the presence of pyridine. A sample of the reaction mixtures was withdrawn and submitted to NMR spectroscopy.

a) Synthesis of the mixed anhydride from propionic acid chloride and 4-nitrobenzoic acid :

Propionic acid chloride (87  $\mu$ L, 1.0 mmol) and 4-nitrobenzoic acid (185 mg, 1.1 mmol) were dissolved in 1 mL dichloromethane. Pyridine (0.1 mL, 1.3 equiv.) was added drop wise. A precipitate formed immediately. The mixture was concentrated by a stream of argon and a portion of the precipitate subjected to <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy.

**b)** Synthesis of the anhydride from propanal and 4-nitrobenzoic acid: Propanal (72  $\mu$ L, 1.0 mmol), TEMPO (3.1 mg, 0.02 mmol, 2 mol%), 4-nitrobezoic acid (185 mg, 1.1 mmol) and pyridine (0.08 mL, 1.0 mmol) were dissolved in 1 mL dry toluene-d<sub>8</sub>. *t*-BuOCl (1.05 mmol) was added at 0 °C. After 1 h the oxidation was complete and no starting material could be detected by GC-MS. The reaction mixture was stirred for another hour, 0.7 mL were filtered into a NMR tube and the <sup>1</sup>H and <sup>13</sup>C NMR were recorded.

### 5. Identification by <sup>1</sup>H NMR



### 5.2 Identification by <sup>13</sup>C NMR



#### 6. Time-resolved NMR investigations with 2,4,6-trichlorobenzoic acid

Exemplary Description of Standard Conditions for NMR investigations:

2,4,6-Trichlorobenzoic acid (124 mg, 0.55 mmol) and TEMPO (1.6 mg, 10  $\mu$ mol, 2 mol%) were suspended in 500  $\mu$ L dry toluene-d<sub>8</sub> in a argon filled Young NMR tube. The aldehyde (0.50 mmol) and pyridine (40  $\mu$ L, 0.50 mmol) were added via Eppendorf pipette. The reaction mixture was cooled to 0 °C and 1.05 equiv. of *t*-butyl hypochlorite (0.53 mmol) were added with an Eppendorf pipette. The reaction process was monitored by <sup>1</sup>H NMR.







#### 7. Description of the preparative experiments with *trans*-cycloalkane-1,2-diols (Table 2)

#### **Description of Standard Conditions for Catalytic Runs**

The conditions for the kinetic resolutions of *trans*-cyclopentane-1,2-diol (*rac*-1a), *trans*-cyclohexane-1,2-diol (*rac*-1b), *trans*-cycloheptane-1,2-diol (*rac*-1c) and *trans*-cyclooctane-1,2-diol (*rac*-1d) with propanal 4a are given exemplarily by the following experimental protocol.

4-nitrobenzoic acid (185 mg, 1.1 mmol) and TEMPO (8 mg, 50  $\mu$ mol, 5 mol%) were suspended in 1 mL dry toluene. Propanal (72  $\mu$ L, 1.0 mmol) and 81  $\mu$ L pyridine (1.0 mmol) were added via Eppendorf pipette. The reaction mixture was cooled to 0 °C and 1.05 equiv. of *t*-butyl hypochlorite (1.05 mmol) were then added with an Eppendorf pipette and allowed to stir for 1 h at 0 °C. After completion of the oxidation of aldehyde to the mixed anhydride the reaction was diluted with 200 mL dry toluene and cooled to 0 °C. Catalyst C (38 mg, 50  $\mu$ mol, 5 mol%) and *trans*-cycloalkane-1,2-diol (1.0 mmol) were added followed by D*i*PEA (170  $\mu$ L, 1.0 mmol). The reaction mixture was quenched with 10 mL methanol and then filtered through 30 g silica gel suspended with EtOAc to remove the catalyst (the silica gel was washed with EtOAc). Purification methods were different for each synthesis and can be found in the corresponding paragraph (see below).

#### Data for the preparative kinetic resolution of *rac*-1b with 4a:

#### **Purification:**

After the filtration the solvents were removed under reduced pressure. The crude product was directly purified by silica gel column chromatography. Eluting with DCM/MeOH/Et<sub>3</sub>N 95:5:0.1 afforded 74 mg (0.43 mmol, 43%) of monopropionate **6b** ( $R_f = 0.59$ ) and 53 mg (0.46 mmol, 46%) of diol **1b** ( $R_f = 0.20$ ). The products were then directly characterized by chiral GC analysis, chiral HPLC analysis and NMR.

#### Data for diol 1b :



Diol *rac*-1b was purchased from Acros Organics at the highest purity grade available and was used without further purifications.

#### Assay of enantiomeric purity.

Enantiomers of diol **1b** were separated by chiral GC employing a 30 m FS-Hydrodex  $\gamma$ -DiMOM column (Macherey-Nagel). T (Injector + Detector) = 250 °C Splitflow = 80 mL/min Precolumn pressure = 0.8 bar Conditions: 100 °C - 240 °C, 10 °C/min Retention Times: R<sub>1</sub> (*S*,*S*) = 28.5 min; R<sub>2</sub> (*R*,*R*) = 27.9 min

#### Data for monopropionate 6b:



#### Assay of enantiomeric purity.

Enantiomers of monoacetate **6b** were separated by chiral GC employing a 30 m FS-Hydrodex  $\gamma$ -DiMO column (Macherey-Nagel). T (Injector + Detector) = 250 °C Splitflow = 80 mL/min Precolumn pressure = 0.8 bar Conditions: 100 °C - 240 °C, 10 °C/min Retention Times: R<sub>1</sub> (*S*,*S*) = 36.7 min; R<sub>2</sub> (*R*,*R*) = 36.9 min

#### **Proof of GC retention times for 6b:**

Racemic *trans*-cyclohexane-1,2-diol (*rac*-1b) (0.345 g, 3.0 mmol) was treated with propionic anhydride (371  $\mu$ L, 4.0 mmol) in the presence of *N*,*N*-dimethylaminopyridine (0.073 g, 0.6 mmol) in 20 mL dichloromethane and the resulting solution was stirred for 3 h at room temperature (25 °C). Dichloromethane was then removed *in vacuo*, and the monopropionate (*rac*-6b) was purified by silica flash gel chromatography (EtOAc, Rf (6b) = 0.59). Isolated *rac*-6b was characterized and then subjected to the GC assay described above to proof the origin of the GC signals.

Analytical data of the product (*rac*-6b) were identical with those reported in the literature.<sup>[5]</sup>

#### Data for the preparative kinetic resolution of *rac*-1a with 4a:

#### **Purification:**

The quenched reaction mixture was directly analyzed by chiral GC without further purification.

#### Data for diol 1a:



Diol *rac*-1a was purchased from Acros Organics at the highest purity grade available and was used without further purifications.

#### Assay of enantiomeric purity.

Enantiomers of diol **1a** were separated by chiral GC employing a 30 m FS-Hydrodex  $\beta$ -6TBDAc column (Macherey-Nagel). T (Injector + Detector) = 250 °C Splitflow = 80 mL/min Precolumn pressure = 0.8 bar Conditions: 100 °C - 180 °C, 2 °C/min Retention Times: R<sub>1</sub>(*S*,*S*) = 26.7 min; R<sub>2</sub>(*R*,*R*) = 27.2 min

#### Data for monopropionate 6a:



#### Assay of enantiomeric purity.

Enantiomers of monoacetate **6a** were separated by chiral GC employing a 30 m FS-Hydrodex  $\beta$ -6TBDAc column (Macherey-Nagel). T (Injector + Detector) = 250 °C Splitflow = 80 mL/min Precolumn pressure = 0.8 bar Conditions: 100 °C - 180 °C, 2 °C/min Retention Times: R<sub>1</sub>(*S*,*S*) = 19.0 min; R<sub>2</sub>(*R*,*R*) = 18.6 min

#### **Proof of GC retention times for 6a:**

Racemic *trans*-cyclopentane-1,2-diol (*rac*-1a) (0.306 g, 3.0 mmol) was treated with propionic anhydride (371  $\mu$ L, 4.0 mmol) in the presence of *N*,*N*-dimethylaminopyridine (0.073 g, 0.6 mmol) in 20 mL dichloromethane and the resulting solution was stirred for 3 h at room temperature (25 °C). Dichloromethane was then removed *in vacuo*, and the monopropionate (*rac*-6a) was purified by silica flash gel chromatography (EtOAc, R<sub>f</sub> (6a) = 0.60). Isolated *rac*-6a was characterized and then subjected to the GC assay described above to proof the origin of the GC signals.

Analytical data:

<sup>1</sup>**H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 4.83 - 4.77 (m, 1 H); 4.11 - 4.02 (m, 1 H); 3.01 - 2.92 (m, 1 H); 2.40 - 2.29 (q, J = 7.7 Hz, 2 H); 2.17 - 2.06 (m, 1 H), 2.06 - 1.95 (m, 1 H); 1.85 - 1.57 (m, 4 H); 1.19 - 1.09 (t, J = 7.7 Hz, 3 H). <sup>13</sup>**C NMR** (150 MHz, CDCl<sub>3</sub>): δ/ppm = 175.7; 83.7; 32.5; 30.0; 27.7; 21.7; 21.6; 9.1.

**C** NMR (150 MHz, CDCI3): o/ppm = 1/5.7; 83.7; 32.5; 30.0; 27.7; 21.7; 21.6; 9.1

**IR** (KBr):  $\tilde{v}$  /cm<sup>-1</sup> = 3443; 2945; 2882; 1736; 1463; 1350; 1276; 1194; 1090; 1038. **HR-MS** (ESI): m/z = 181.0835 [M+Na]<sup>+</sup> (calc. m/z = 181.0835).

#### Data for the preparative kinetic resolution of *rac*-1c with 4a:

#### **Purification:**

After the filtration the solvents were removed under reduced pressure. The crude product was directly purified by silica gel column chromatography. Eluting with 5% MeOH/DCM afforded 79 mg (0.43 mmol, 43%) of monopropionate **6a** ( $R_f$  = 0.53) and 63 mg (0.48 mmol, 48%) of diol **1a** ( $R_f$  = 0.14). The products were then directly characterized by chiral GC analysis, chiral HPLC analysis and NMR.

#### Data for diol 1c :



Diol *rac*-1c was synthesized as described in chapter 3.

#### Assay of enantiomeric purity.

Enantiomers of diol **1c** were separated by chiral GC employing a 30 m FS-Hydrodex  $\beta$ -6TBDM column (Macherey-Nagel). T (Injector + Detector) = 250 °C Splitflow = 80 mL/min Precolumn pressure = 0.8 bar Conditions: 140 °C isotherm Retention Times: R<sub>1</sub>(*S*,*S*) = 10.4 min; R<sub>2</sub>(*R*,*R*) = 11.0 min

#### Data for monopropionate 6c:



#### Assay of enantiomeric purity.

Enantiomers of monoacetate **6c** were separated by chiral HPLC employing a Chiralpak IA column (Daicel). Eluent: Hexane/2-Propanol 90:10 Flow: 1.00 ml/min. UV-detector  $\lambda = 220$  nm and refractometer Retention Times:  $R_1(S,S) = 10.3$  min;  $R_2(R,R) = 13.0$  min

#### **Proof of HPLC retention times for 6c:**

Racemic *trans*-cycloheptane-1,2-diol (*rac*-1c) (0.390 g, 3.0 mmol) was treated with propionic anhydride (371  $\mu$ L, 4.0 mmol) in the presence of *N*,*N*-dimethylaminopyridine (0.073 g, 0.6 mmol) in 20 mL dichloromethane and the resulting solution was stirred for 3 h at room temperature (25 °C). Dichloromethane was then removed *in vacuo*, and the monopropionate (*rac*-6c) was purified by silica flash gel chromatography (EtOAc, R<sub>f</sub> (6c) = 0.46). Isolated *rac*-6c was characterized and then subjected to the HPLC assay described above to proof the origin of the HPLC signals.

Analytical data:

<sup>1</sup>**H** NMR (400 MHz, CDCl<sub>3</sub>): δ/ppm = 4.75 – 4.67 (m, 1 H); 3.78 - 3.70 (m, 1 H); 2.75 - 2.69 (s, 1 H); 2.42 - 2.32 (q, J = 7.5, 2 H); 1.91 - 1.44 (m, 10 H); 1.19 - 1.11 (t, J = 7.5 Hz, 1 H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ/ppm = 175.1; 81.8; 75.9; 32.8; 30.3; 28.3; 27.9; 23.0; 22.8; 9.3.

**IR** (KBr):  $\tilde{v}$  /cm<sup>-1</sup> = 3449; 2935; 2863; 1734; 1461; 1369; 1275; 1200; 1082; 1028. **HR-MS (ESI):** m/z = 209.1148 [M+Na]<sup>+</sup> (calc. m/z = 209.1148).

#### Data for the preparative kinetic resolution of *rac*-1d with 4a:

#### **Purification:**

After the filtration the solvents were removed under reduced pressure. The crude product was directly purified by silica gel column chromatography. Eluting with EtOAc afforded 95 mg (0.47 mmol, 47%) of monopropionate **6d** ( $R_f$ = 0.80) and 56 mg (0.39 mmol, 39%) of diol **1d** ( $R_f$ = 0.24). The products were then directly characterized by chiral GC analysis, chiral HPLC analysis and NMR.





Diol *rac*-1d was synthesized as described in chapter 3.

#### Assay of enantiomeric purity.

Enantiomers of diol **1d** were separated by chiral GC employing a 30 m FS-Hydrodex  $\beta$ -6TBDM column (Macherey-Nagel). T (Injector + Detector) = 250 °C Splitflow = 80 mL/min Precolumn pressure = 0.8 bar Conditions: 80 °C - 130 °C, 0.4 °C/min Retention Times: R<sub>1</sub> (*S*,*S*) = 105.9 min; R<sub>2</sub> (*R*,*R*) = 107.1 min

#### Data for monopropionate 6d:



#### Assay of enantiomeric purity.

Enantiomers of monoacetate **6d** were separated by chiral HPLC employing a Chiralpak IA column (Daicel).

Eluent: Hexane/2-Propanol 90:10

Flow: 1.00 ml/min.

UV-detector  $\lambda = 220$  nm and refractometer

Retention Times:  $R_1(S,S) = 16.4 \text{ min}; R_2(R,R) = 16.9 \text{ min}$ 

#### **Proof of HPLC retention times for 6d:**

Racemic *trans*-cyclooctane-1,2-diol (*rac*-1d) (0.432 g, 3.0 mmol) was treated with propionic anhydride (371  $\mu$ L, 4 mmol) in the presence of *N*,*N*-dimethylaminopyridine (0.073 g, 0.6 mmol) in 20 mL dichloromethane and the resulting solution was stirred for 3 h at room temperature (25 °C). Dichloromethane was then removed *in vacuo*, and the monopropionate (*rac*-6d) was purified by silica flash gel chromatography (EtOAc, R<sub>f</sub> (6d) = 0.80). Isolated *rac*-6d was characterized and then subjected to the HPLC assay described above to proof the origin of the HPLC signals.

Analytical data:

<sup>1</sup>**H** NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 5.10 – 5.01 (m, 1 H); 3.99 – 3.92 (m, 1 H); 2.42 – 2.29 (m, 3 H); 2.13 – 2.00 (m, 1 H); 1.85 – 1.48 (m, 11 H); 1.19 – 1.11 (t, J = 7.6 Hz, 3 H). <sup>13</sup>**C** NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 174.1; 76.8; 71.7; 30.3; 27.9; 27.8, 27.0; 25.5; 24.5; 21.8; 9.1.

**IR** (KBr):  $\tilde{v}$  /cm<sup>-1</sup> = 3456; 2929; 2861; 1732; 1463; 1359; 1277; 1191; 1081; 1030. **HR-MS (ESI):** m/z = 223.1303 [M+Na]+ (calc. m/z = 223.1305).

# 8. Description of the preparative experiments with *trans*-cyclohexane-1,2-diol using the aldehydes 4b-i (Table 3)

The conditions for the preparative kinetic resolution of **7a** with **4b–i** are given exemplary by the following experimental protocol [Values in blue: double amount of generated anhydride]. 4-nitrobenzoic acid (185 mg, 1.1 mmol) [368 mg, 2.2 mmol] and TEMPO (8 mg, 50 µmol, 5 mol%) [16 mg, 100 µmol, 5 mol%] were suspended in 1 mL [2 mL]\* dry toluene. Additionally the aldehyde (1.0 mmol) [2 mmol] and 81 µL (1.0 mmol) [162 µL, 2.0 mmol] pyridine were added via Eppendorf pipette. The reaction mixture was cooled to 0 °C and 1.05 equiv. of *t*-butyl hypochlorite (1.05 mmol) [2.1 mmol] was then added with an Eppendorf pipette and allowed to stir 1 h at 0 °C. After completion of the oxidation and conversion of the aldehyde to the mixed anhydride the reaction mixture was filled up to 200 mL with dry toluene and cooled to 0 °C. Catalyst **B** (38 mg, 50 µmol, 5 mol%) and *trans*-cycloalkane-1,2-diol (116 mg, 1.0 mmol) were added in one portion followed by D*i*PEA (170 µL, 1.0 mmol) [340 µL, 2.0 mmol]. The reaction mixture was quenched with 10 mL methanol and then filtered using 30 g silica gel suspended with EtOAc to remove the catalyst (the silica gel was washed with EtOAc). Purification methods were different for each synthesis and can be found in the corresponding paragraph (see below).

\* For aldehydes **4g–i** a solvent volume of 20 mL was used.

#### Data for the preparative kinetic resolution of racemic 1b with 4b:

#### **Purification:**

After the filtration the solvents were removed under reduced pressure. The crude product was directly purified by silica gel column chromatography. Eluting with DCM/MeOH/Et<sub>3</sub>N 95:5:0.1 afforded 113 mg (0.42 mmol, 42%) of monoprotected diol **9b** ( $R_f$ = 0.67) and 56 mg (0.48 mmol, 48%) of diol **1b** ( $R_f$ = 0.20). The products were then directly characterized by chiral GC analysis and NMR.

#### Data for monodecanoate 9b:



#### Assay of enantiomeric purity.

Enantiomers of monoprotected diol **9b** were separated by chiral HPLC employing a Chiralpack IC column (Daicel).

Eluent: Hexane/2-Propanol 95:5 Flow: 1 mL/min UV-detector  $\lambda = 220$  nm and refractometer Retention Times: R<sub>1</sub>(*S*,*S*) = 12.8 min; R<sub>2</sub>(*R*,*R*) = 13.5 min

#### **Proof of HPLC retention times for 9b:**

4-nitrobenzoic acid (185 mg, 1.1 mmol) and TEMPO (8 mg, 50  $\mu$ mol, 5 mol%) were suspended in 1 mL dry toluene. Additionally the aldehyde (1.0 mmol) and 81  $\mu$ L (1.0 mmol) pyridine were added via Eppendorf pipette. The reaction mixture was cooled to 0 °C and 1.05 equiv. of *t*-butyl hypochlorite (1.05 mmol) was then added with an Eppendorf pipette and allowed to stir 1 h at 0 °C. 4-(Dimethylamino)-pyridine (12 mg, 0.1 mmol, 10 mol%) and

*trans*-cycloalkan-1,2-diol (116 mg, 1.0 mmol) were added in one portion followed by D*i*PEA (170  $\mu$ L, 1.0 mmol) and stirred at rt. 6 h. The solvents were then removed *in vacuo*, and *rac*-**9b** was purified by silica flash gel chromatography (Hexane/Et<sub>2</sub>O/Et<sub>3</sub>N 1:1:0.1, R<sub>f</sub> (**9b**) = 0.28). Isolated *rac*-**9b** was characterized and then subjected to the HPLC assay described above to proof the origin of the HPLC signals.

Analytical data: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 4.64 – 4.52 (m, 1 H); 3.61 – 3.51 (m, 1 H); 2.39 – 2.28 (t, J = 7.8 Hz, 2 H); 2.13 – 1.98 (m, 2 H); 1.94 – 1.89 (s, 1 H); 1.78 – 1.68 (m, 2 H); 1.67 – 1.57 (m, 2 H); 1.40 – 1.20 (m, 16 H); 0.94 – 0.82 (t, J = 7.8 Hz, 3 H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 174.3; 78.1; 73.0; 34.7; 33.1; 31.9; 30.0; 29.4; 29.3; 29.1; 25.1; 23.9; 23.8; 22.7; 14.2. IR (KBr):  $\tilde{\nu}$ /cm<sup>-1</sup> = 3452; 2928; 2856; 1735; 1454; 1351; 1248; 1180; 1076; 1020; 852. HR-MS (ESI): m/z = 293.2088 [M+Na]<sup>+</sup> (calc. m/z = 293.2087).

#### Data for the preparative kinetic resolution of racemic 1b with 4c:

#### **Purification:**

After the filtration the solvents were removed under reduced pressure. The crude product was directly purified by silica gel column chromatography. Eluting with DCM/MeOH/Et<sub>3</sub>N 95:5:0.1 afforded 86 mg (0.43 mmol, 43%) of monoprotected diol **9c** ( $R_f$  = 0.77) and 53 mg (0.46 mmol, 46%) of diol **1b** ( $R_f$  = 0.20). The products were then directly characterized by chiral GC analysis and NMR.

#### Data for monoisovalerate 9c:



Assay of enantiomeric purity.

Enantiomers of monoprotected diol 9c were separated by chiral HPLC employing a Chiralpack IC column (Daicel).

Eluent: Hexane/2-Propanol 90:10 Flow: 1 mL/min UV-detector  $\lambda = 220$  nm and refractometer Retention Times: R<sub>1</sub> (*S*,*S*) = 7.8 min; R<sub>2</sub> (*R*,*R*) = 8.4 min

#### **Proof of HPLC retention times for 9c:**

4-nitrobenzoic acid (185 mg, 1.1 mmol) and TEMPO (8 mg, 50 µmol, 5 mol%) were suspended in 1 mL dry toluene. Additionally the aldehyde (1.0 mmol) and 81 µL (1.0 mmol) pyridine were added via Eppendorf pipette. The reaction mixture was cooled to 0 °C and 1.05 equiv. of *t*-butyl hypochlorite (1.05 mmol) was then added with an Eppendorf pipette and allowed to stir 9 h at 0 °C. 4-(Dimethylamino)-pyridine (12 mg, 0.1 mmol, 10 mol%) and *trans*-cycloalkan-1,2-diol (116 mg, 1.0 mmol) were added in one portion followed by D*i*PEA (170 µL, 1 mmol) and stirred at rt. 6 h. The solvents were then removed *in vacuo*, and *rac*-9c was purified by silica flash gel chromatography (Hexane/Et<sub>2</sub>O/Et<sub>3</sub>N 3:7:0.1, Rf (9c) = 0.40). Isolated *rac*-9c was characterized and then subjected to the HPLC assay described above to proof the origin of the HPLC signals.

Analytical data: <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 4.68 – 4.51 (m, 1 H); 3.64 – 3.47 (m, 1 H); 2.24 – 2.16 (t, J = 6.3 Hz, 2 H); 2.13 – 2.01 (m, 3 H); 1.81 – 1.61 (m, 2 H); 1.44 – 1.22 (m, 4 H); 1.03 – 0.92 (d, J = 6.3 Hz, 6 H). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 172.8; 77.2; 72.1; 43.0; 32.3; 29.4; 25.1; 23.1; 21.6. IR (KBr):  $\tilde{v}$ /cm<sup>-1</sup> = 3445; 2939; 2868; 1731; 1452; 1357; 1293; 1193; 1078; 1022. HR-MS (ESI): m/z = 223.1308 [M+Na]<sup>+</sup> (calc. m/z = 223.1305).

#### Data for the preparative kinetic resolution of racemic 1b with 4d:

#### **Purification:**

After the filtration the solvents were removed under reduced pressure. The crude product was directly purified by silica gel column chromatography. Eluting with DCM/MeOH/Et<sub>3</sub>N 95:5:0.1 afforded 75 mg (0.40 mmol, 40%) of monoprotected diol **9d** ( $R_f$  = 0.79) and 50 mg (0.43 mmol, 43%) of diol **1b** ( $R_f$  = 0.20). The products were then directly characterized by chiral GC analysis and NMR.

#### Data for monoisobutyrate 9d:



#### Assay of enantiomeric purity.

Enantiomers of diol **9d** were separated by chiral GC employing a 30 m FS-Hydrodex  $\gamma$ -DiMOM column (Macherey-Nagel). T (Injector + Detector) = 250 °C Splitflow = 80 mL/min

Precolumn pressure = 0.8 bar Conditions: 100 °C – 240 °C, 10 °C/min Retention Times:  $R_1(S,S) = 37.1$  min;  $R_2(R,R) = 37.2$  min

#### **Proof of HPLC retention times for 9d:**

4-nitrobenzoic acid (185 mg, 1.1 mmol) and TEMPO (8 mg, 50 µmol, 5 mol%) were suspended in 1 mL dry toluene. Additionally the aldehyde (1.0 mmol) and 81 µL (1.0 mmol) pyridine were added via Eppendorf pipette. The reaction mixture was cooled to 0 °C and 1.05 equiv. of *t*-butyl hypochlorite (1.05 mmol) was then added with an Eppendorf pipette and allowed to stir 18 h at 0 °C. 4-(Dimethylamino)-pyridine (12 mg, 0.1 mmol, 10 mol%) and *trans*-cycloalkan-1,2-diol (116 mg, 1.0 mmol) were added in one portion followed by D*i*PEA (170 µL, 1.0 mmol) and stirred at rt 6 h. The solvents were then removed *in vacuo*, and *rac*-9d was purified by silica flash gel chromatography (Hexane/Et<sub>2</sub>O/Et<sub>3</sub>N 3:7:0.1, Rf (9d) = 0.29). Isolated *rac*-9d was characterized and then subjected to the HPLC assay described above to proof the origin of the HPLC signals.

Analytical data of the monoacylated product (rac-9d) were identical with those reported in the literature.<sup>[6]</sup>

#### Data for the preparative kinetic resolution of racemic 1b with 4e:

#### **Purification:**

After the filtration the solvents were removed under reduced pressure. The crude product was directly purified by silica gel column chromatography. Eluting with DCM/MeOH/Et<sub>3</sub>N 95:5:0.1 afforded 79 mg (0.35 mmol, 35%) of monoprotected diol **9e** ( $R_f$  = 0.75) and 43 mg (0.37 mmol, 37%) of diol **1b** ( $R_f$  = 0.20). The products were then directly characterized by chiral GC analysis and NMR.

#### Data for monocyclohexanecarboxylate 9e:



#### Assay of enantiomeric purity.

Enantiomers of monoprotected diol **9e** were separated by chiral HPLC employing a Chiralpack IC column (Daicel).

Eluent: Hexane/2-Propanol 90:10

Flow: 1 mL/min

UV-detector  $\lambda = 220$  nm and refractometer Retention Times:  $R_1(S,S) = 9.2$  min;  $R_2(R,R) = 9.8$  min

#### **Proof of HPLC retention times for 9e:**

4-nitrobenzoic acid (185 mg, 1.1 mmol) and TEMPO (8 mg, 50 µmol, 5 mol%) were suspended in 1 mL dry toluene. Additionally the aldehyde (1.0 mmol) and 81 µL (1.0 mmol) pyridine were added via Eppendorf pipette. The reaction mixture was cooled to 0 °C and 1.05 equiv. of *t*-butyl hypochlorite (1.05 mmol) was then added with an Eppendorf pipette and allowed to stir 18 h at 0 °C. 4-(Dimethylamino)-pyridine (12 mg, 0.1 mmol, 10 mol%) and *trans*-cycloalkan-1,2-diol (116 mg, 1.0 mmol) were added in one portion followed by D*i*PEA (170 µL, 1.0 mmol) and stirred at rt. 6 h. The solvents were then removed *in vacuo*, and *rac*-**9e** was purified by silica flash gel chromatography (Hexane/Et<sub>2</sub>O/Et<sub>3</sub>N 3:7:0.1, Rf(**9e**) = 0.43). Isolated racemic *rac*-**9e** was characterized and then subjected to the HPLC assay described above to proof the origin of the HPLC signals.

#### Analytical data:

<sup>1</sup>**H NMR** (400 MHz, CDCl<sub>3</sub>): δ/ppm = 4.63 – 4.49 (m, 1 H); 3.64 – 4.48 (m, 1 H); 2.44 – 2.28 (m, 1 H); 2.14 – 1.87 (m, 5 H); 1.82 – 1.61 (m, 5 H); 1.50 – 1.24 (m, 8 H). <sup>13</sup>**C NMR** (150 MHz, CDCl<sub>3</sub>): δ/ppm = 176.5; 77.8; 72.9; 43.4; 33.0; 29.9; 29.1; 29.0; 25.7; 25.4; 23.9; 23.7.

**IR** (KBr):  $\tilde{v}$  /cm<sup>-1</sup> = 3451; 2934; 2858; 1729; 1451; 1379; 1248; 1174; 1039; 733. **HR-MS** (ESI): m/z = 249.1461 [M+Na]<sup>+</sup> (calc. m/z = 249.1461).

#### Data for the preparative kinetic resolution of racemic 1b with 4f:

Data for monopivalate 9f:



#### Assay of enantiomeric purity. Enantiomers of diol 9f were separated by chiral GC employing a 30 m FS-Hydrodex $\gamma$ -DiMOM column (Macherey-Nagel). T (Injector + Detector) = 250 °C Splitflow = 80 mL/min Precolumn pressure = 0.8 bar Conditions: 100 °C, 30 min; 100 °C – 240 °C, 5 °C/min Retention Times: R<sub>1</sub> (*S*,*S*) = 40.3 min; R<sub>2</sub> (*R*,*R*) = 40.4 min

#### **Proof of GC retention times for 8e:**

Racemic *trans*-cyclohexane-1,2-diol (*rac*-1b) (0.345 g, 3.0 mmol) was treated with pivalic anhydride (811  $\mu$ L, 4.0 mmol) in the presence of *N*,*N*-dimethylaminopyridine (0.073 g, 0.6 mmol) in 20 mL dichloromethane and the resulting solution was stirred for 3 h at room temperature (25 °C). Dichloromethane was then removed *in vacuo*, and the monoprotected (*rac*-9f) was purified by silica flash gel chromatography. Isolated *rac*-9f was characterized and then subjected to the GC assay described above to proof the origin of the GC signals.

Analytical data of the monoacylated product (rac-9f) were identical with those reported in the literature.<sup>[7]</sup>

#### Data for the preparative kinetic resolution of racemic 1b with 4g:

#### **Purification:**

After the filtration the solvents were removed under reduced pressure. The crude product was directly purified by silica gel column chromatography. Eluting with DCM/MeOH/Et<sub>3</sub>N 95:5:0.1 afforded 109 mg (0.44 mmol, 44%) of monoprotected diol **4g** ( $R_f$ = 0.80) and 51 mg (0.44 mmol, 44%) of diol **1b** ( $R_f$ = 0.20). The products were then directly characterized by chiral GC analysis and NMR.

#### Data for monophenylpropionate 9g:



#### Assay of enantiomeric purity.

Enantiomers of monoprotected diol **9g** were separated by chiral HPLC employing a Chiralpack IB column (Daicel). Eluent: Hexane/2-Propanol 90:10 Flow: 0.7 mL/min UV-detector  $\lambda = 220$  nm and refractometer Retention Times: R<sub>1</sub>(*S*,*S*) = 11.1 min; R<sub>2</sub>(*R*,*R*) = 9.4 min

#### **Proof of HPLC retention times for 9g:**

4-nitrobenzoic acid (185 mg, 1.1 mmol) and TEMPO (8 mg, 50 µmol, 5 mol%) were suspended in 20 mL dry toluene. Additionally the aldehyde (1.0 mmol) and 81 µL (1.0 mmol) pyridine were added via Eppendorf pipette. The reaction mixture was cooled to 0 °C and 1.05 equiv. of *t*-butyl hypochlorite (1.05 mmol) was then added with an Eppendorf pipette and allowed to stir 18 h at 0 °C. 4-(Dimethylamino)-pyridine (12 mg, 0.1 mmol, 10 mol%) and *trans*-cycloalkan-1,2-diol (116 mg, 1.0 mmol) were added in one portion followed by DiPEA (170 µL, 1.0 mmol) and stirred at rt 6 h. The solvents were then removed *in vacuo*, and (±)-**8f** was purified by silica flash gel chromatography (Hexane/Et<sub>2</sub>O/Et<sub>3</sub>N 3:7:0.1, R<sub>f</sub>(**9g**) = 0.64). Isolated *rac*-**9g** was characterized and then subjected to the HPLC assay described above to proof the origin of the HPLC signals.

Analytical data:

<sup>1</sup>**H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$ /ppm = 7.33 – 7.19 (m, 5 H); 4.62 – 4.46 (m, 1 H); 3.05 – 2.09 (t, J = 7.6 Hz, 2 H); 2.75 – 2.62 (t, J = 7.6 Hz, 2 H); 2.07 – 1.91 (m, 2 H); 1.77 – 1.63 (m, 2 H); 1.39 – 1.15 (m, 4 H).

<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ/ppm = 173.1; 140.4; 128.6; 128.3; 126.4; 78.4; 72.6; 36.1; 32.8; 31.1; 30.0; 23.9; 23.8.

**IR** (KBr):  $\tilde{v}$  /cm<sup>-1</sup> = 3446; 2939; 2863; 1730; 1453; 1371; 1288;1263; 1181; 1077; 1009; 912; 733; 699.

**HR-MS (ESI):**  $m/z = 271.1306 [M+Na]^+$  (calc. m/z = 271.1305).

#### Data for the preparative kinetic resolution of racemic 1b with 4h:

#### **Purification:**

After the filtration the solvents were removed under reduced pressure. The crude product was directly purified by silica gel column chromatography. Eluting with DCM/MeOH/Et<sub>3</sub>N 95:5:0.1 afforded 63 mg (0.27 mmol, 27%) of monoprotected diol **9h** ( $R_f$ = 0.82) and 67 mg (0.58 mmol, 58%) of diol **1b** ( $R_f$ = 0.20). The products were then directly characterized by chiral GC analysis and NMR.

#### Data for monophenylacetate 9h:



#### Assay of enantiomeric purity.

Enantiomers of monoprotected diol **9h** were separated by chiral HPLC employing a Chiralpack IB column (Daicel).

Eluent: Hexane/2-Propanol 90:10 Flow: 0.7 mL/min UV-detector  $\lambda = 220$  nm and refractometer Retention Times: R<sub>1</sub>(*S*,*S*) = 14.0 min; R<sub>f</sub>(*R*,*R*) = 10.7 min

#### **Proof of HPLC retention times for 9h:**

4-nitrobenzoic acid (185 mg, 1.1 mmol) and TEMPO (8 mg, 50  $\mu$ mol, 5 mol%) were suspended in 20 mL dry toluene. Additionally the aldehyde (1.0 mmol) and 81  $\mu$ L (1.0

mmol) pyridine were added via Eppendorf pipette. The reaction mixture was cooled to 0 °C and 1.05 equiv. of *t*-butyl hypochlorite (1.05 mmol) was then added with an Eppendorf pipette and allowed to stir 18 h at 0 °C. 4-(Dimethylamino)-pyridine (12 mg, 0.1 mmol, 10 mol%) and *trans*-cycloalkan-1,2-diol (116 mg, 1.0 mmol) were added in one portion followed by DiPEA (170 µL, 1.0 mmol) and stirred at rt 6 h. The solvents were then removed *in vacuo*, and *rac*-9h was purified by silica flash gel chromatography (Hexane/Et<sub>2</sub>O/Et<sub>3</sub>N 3:7:0.1, R<sub>f</sub> (9h) = 0.64). Isolated *rac*-9h was characterized and then subjected to the HPLC assay described above to proof the origin of the HPLC signals.

Analytical data of the monoacylated product (*rac*-**9h**) were identical with those reported in the literature.<sup>[5]</sup>

#### Data for the preparative kinetic resolution of racemic 1b with 4i:

Data for monobenzoate 9i:



Assay of enantiomeric purity.

Enantiomers of monoprotected diol **9i** were separated by chiral GC employing a 30 m FS-Hydrodex  $\beta$  - TBDAc column (Macherey-Nagel). T (Injector + Detector) = 250 °C Splitflow = 80 mL/min Precolumn pressure = 0.8 bar Conditions: 100 °C - 200 °C, 1.4 °C/min Retention Times: R<sub>1</sub> (*S*,*S*) = 70.3 min; R<sub>2</sub> (*R*,*R*) = 70.5 min

#### **Proof of GC retention times for 9i:**

Racemic *trans*-cyclohexane-1,2-diol (*rac*-1b) (0.345 g, 3.0 mmol) was treated with benzoic anhydride (755  $\mu$ L, 4.0 mmol) in the presence of *N*,*N*-dimethylaminopyridine (0.073 g, 0.6 mmol) in 20 mL dichloromethane and the resulting solution was stirred for 3 h at room temperature (25 °C). Dichloromethane was then removed *in vacuo*, and the monoprtected (*rac*-9i) was purified by silica flash gel chromatography. Isolated *rac*-9i) was characterized and then subjected to the GC assay described above to proof the origin of the GC signals.

Analytical data of the monoacylated product (rac-9i) were identical with those reported in the literature.<sup>[8]</sup>

#### 9. Description of the preparative experiments with multicatalyst C

4-nitrobenzoic acid (185 mg, 1.1 mmol) and C (45 mg, 50 µmol, 5 mol%) were suspended in 1 mL dry toluene. Propanal (72 µL, 1.0 mmol) and 81 µL pyridine (1.0 mmol) were added via Eppendorf pipette. The reaction mixture was cooled to 0 °C and 1.05 equiv. of *t*-butyl hypochlorite (1.05 mmol) was then added with an Eppendorf pipette and allowed to stir 1 h at 0 °C. After completion of the oxidation of aldehyde to the mixed anhydride the reaction was diluted with 200 mL dry toluene and cooled to 0 °C. Trans-cyclohexane-1,2-diol (116 mg, 1.0 mmol) were added in one portion followed by D*i*PEA (680 µL, 4.0 mmol). The reaction mixture was quenched with 10 mL methanol and then filtered using 30 g silica gel suspended with EtOAc to remove the catalyst (the silica gel was washed with EtOAc). The solvents were then removed *in vacuo* and **6b** was purified as described in chapter 7. 71 mg (0.41 mmol, 41%) of monoprotected diol **6b** and 50 mg (0.43 mmol, 43%) of diol **2b** were obtained. The products were then directly characterized by chiral GC analysis and NMR.

#### 10. NMR spectra















#### 11. Literature

[1] C. E. Müller, R. Hrdina, R. C. Wende and P. R. Schreiner, *Chem.-Eur. J.*, 2011, **17**, 6309-6314.

[2] C. E. Müller, L. Wanka, K. Jewell and P. R. Schreiner, *Angew. Chem. Int. Ed.*, 2008, 47, 6180-6183.

[3] Autorenkollektiv. Organikum: Organisch-chemisches Grundpraktikum, 19th ed.; Deutscher Verlag der Wissenschaften: Leipzig, **1993**.

[4] H. Toledo, E. Pisarevsky, A. Abramovich and A. M. Szpilman, *Chem. Commun.*, 2013, **49**, 4367-4369.

[5] N. Iranpoor, H. Firouzabadi, A. Safavi, M. Shekarriz, Synth. Commu., 2002, **32**, 2287-2293.

[6] T. Kawabata, M. Nagato, K. Takasu, K. Fuji, J. Am. Chem. Soc., 1977, 119, 3169-3170.

[7] R. Hrdina, C. E. Müller, P. R. Schreiner, Chem. Commun., 2010, 46, 2689-2690.

[8] Y. Matsumura, T. Maki, S. Murakami, O. Onomura, J. Am. Chem. Soc., 2003, 125, 2052-2053.