Supporting Information

trans-Selective and Switchable Arene Hydrogenation of Phenol Derivatives

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1. Materials and Methods

Unless otherwise noted, all reactions were carried out under an atmosphere of argon in oven-dried glassware. Reaction temperatures are reported as the temperature of the bath / metal block surrounding the vessel unless otherwise stated. The solvents used were purified by distillation over the drying agents indicated in parentheses: n-hexane (CaH$_2$), dichloromethane (CaH$_2$), diethylether (Na-benzophenone), THF (Na-benzophenone). Dichloroethane (4Å), 1,4-dioxane (4Å), ethyl acetate (4Å), methanol (3Å) and ethanol (4Å) were purchased as dry solvents from commercial suppliers and stored over molecular sieves. n-Heptane (Acros Organics, 99+%) and iso-propanol (Fisher Scientific, 99.8%) were used as received from supplier.

All hydrogenation reactions were carried out in Berghof High Pressure Reactors using hydrogen gas. Commercially available chemicals were obtained from Acros Organics, Aldrich Chemical Co., Strem Chemicals, Alfa Aesar, ABCR, Combi-Blocks, Chempur and TCI Europe and used as received unless otherwise stated. Palladium/Al$_2$O$_3$ was obtained from Johnson Matthey 5 wt% Palladium on alumina A302999-5; CODE: S4020; 10 g on dry basis; Lot: C-15059; JM Order: 7248; %water: 2.01. Analytical thin layer chromatography was performed on Polygram SIL G/UV254 plates. Visualization was accomplished with short wave UV light, and/or KMnO$_4$ and ninhydrin staining solutions followed by heating. Flash chromatography was performed on Merck silica gel (40–63 mesh) by standard technique eluting with solvents as indicated.

GC-MS spectra were recorded on an Agilent Technologies 7890A GC-system with an Agilent 5975C VL MSD or an Agilent 5975 inert Mass Selective Detector (EI) and a HP-5MS column (0.25 mm x 30 m, film: 0.25 µm). The major signals are quoted in m/z with the relative intensity in parentheses. The method indicated as ‘50_40’ starts with the injection temperature T$_0$ (50 °C); after holding this temperature for 3 min, the column is heated by 40 °C/min to temperature T$_1$ (290 °C or 320 °C). GC-FID analysis was undertaken on an Agilent Technologies 6890A equipped with an HP-5 quartz column (0.32 mm x 30 m, film: 0.25 µm) using flame ionization detection. Method: Initial temperature 50 °C, hold 3 min, increment 40 °C/min, final temperature 280 °C, hold 3 min. High resolution mass spectra (HRMS) were obtained by the MS service of the Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, using electrospray ionisation (ESI) on a Bruker Daltonics MicroTof spectrometer. Infrared spectra were recorded on a Shimadzu FTIR 8400S spectrometer as neat compound. The wave numbers ($\tilde{\nu}$) of recorded IR-signals are quoted in cm$^{-1}$.

$^1$H and $^{13}$C, $^{19}$F and $^{11}$B NMR spectra were recorded on a Bruker AV 300 or AV 400, Varian 500 MHz INOVA or Varian Unity plus 600 in the indicated solvents. Chemical shifts (δ) are given in ppm relative to TMS. The residual solvent signals were used as references and the
chemical shifts converted to the TMS scale (CDCl₃: δ_H = 7.26 ppm, δ_C = 77.16 ppm; methanol-
-d₄: δ_H = 3.31 ppm, δ_C = 49.00 ppm; acetone-d₆: δ_H = 2.05 ppm, δ_C = 29.84 ppm; CD₃CN: δ_H =
1.94 ppm, δ_C = 1.32 ppm; toluene-d₈: δ_H = 7.09, 7.01, 6.97 and 2.08 ppm, δ_C = 137.48, 128.87,
127.96, 125.13 and 20.43 ppm; DMSO-d₆: δ_H = 2.50 ppm, δ_C = 39.52 ppm).¹¹^F and¹¹^B NMR
spectra are not calibrated by an internal reference. The multiplicities of the signals are reported
as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), p (pentet), hept (heptet) and
m (multiplet). Coupling constants (J) are quoted in Hz.

Data sets for compounds 2f, 2q, 2m and 2o were collected with a Bruker D8 Venture CMOS
diffractometer. Programs used: data collection: APEX3 V2016.1-0¹ (Bruker AXS Inc., 2016);
cell refinement: SAINT V8.37A (Bruker AXS Inc., 2015); data reduction: SAINT V8.37A
(Bruker AXS Inc., 2015); absorption correction, SADABS V2014/7 (Bruker AXS Inc., 2014);
structure solution SHELXT-2015² (Sheldrick, G. M. Acta Cryst., 2015, A71, 3-8); structure
refinement SHELXL-2015³ (Sheldrick, G. M. Acta Cryst., 2015, C71 (1), 3-8) and graphics,
XP⁴ (Version 5.1, Bruker AXS Inc., Madison, Wisconsin, USA, 1998). R-values are given for
observed reflections, and wR² values are given for all reflections.

¹APEX3 (2016), SAINT (2015) and SADABS (2015), Bruker AXS Inc., Madison, Wisconsin, USA.
² Sheldrick, G. M., SHELXT – Integrated space-group and crystal-structure determination, Acta Cryst., 2015,
A71, 3-8.
³ Sheldrick, G.M., Crystal structure refinement with SHELXL, Acta Cryst., 2015, C71 (1), 3-8.
⁴ XP – Interactive molecular graphics, Version 5.1, Bruker AXS Inc., Madison, Wisconsin, USA, 1998.
2. **Preparation of Starting Materials**

All used starting materials are commercially available and were used without further purification.

3. **Optimization of Reaction Conditions**

*General Procedure*

A 4 mL screw-cap glass vial, equipped with a magnetic stirring bar, was charged with catalyst, p-cresol (0.1 mmol, 1.0 equiv.) and solvent (as indicated, 1.0 mL). The prepared glass vial was placed in a 150 mL stainless steel autoclave under air. The autoclave was pressurized and depressurized with hydrogen gas three times before the indicated pressure was set. The reaction mixture was stirred at the indicated temperature overnight. After the autoclave was carefully depressurized, DMAP (0.01 mmol, 0.1 equiv.), imidazole (0.45 mmol, 4.5 equiv.), TBSCI (0.3 mmol, 3.0 equiv.) and dichloromethane (1.0 mL, 0.1 M) were added and the mixture was stirred at 40 °C overnight. After full conversion of the cyclohexanol to the corresponding silyl ether (indicated by GC-MS analysis), mesitylene (14 μL, 0.101 mmol) was added as internal standard and the mixture was stirred vigorously for 5 min. After filtration over Whatman® filter, conversion, yield and diastereomeric ratio (d.r.) were determined by GC-FID analysis.
Table S1. Screening of palladium catalysts.

| entry | catalyst          | conversion [%] | yield 4a [%] | yield 2a-Si [%] (d.r.) |
|-------|------------------|----------------|--------------|------------------------|
| 1     | 5 wt% Pd/C       | 100            | 31           | 69 (69:31)             |
| 2     | 5 wt% Pd/C_{ox.} | 100            | traces       | 98 (50:50)             |
| 3     | 5 wt% Pd/Al₂O₃  | 100            | 0            | 99 (79:21)             |
| 4     | 0.5 wt% Pd/Al₂O₃| 100            | traces       | 96 (81:19)             |
| 5     | 5 wt% Pd/SiO₂    | 77             | 77           | 0                      |
| 6     | 5 wt% Pd/CaCO₃  | 70             | 60           | 10 (61:39)             |
| 7     | 20 wt% Pd(OH)₂/C | 100            | 48           | 52 (40:60)             |

Reaction conditions: 1a (0.1 mmol, 1.0 equiv.), n-heptane (1.0 mL, 0.1 M). TBS-protection after hydrogenation. Conversion of p-cresol. Yields and d.r. values (trans/cis) determined by GC-FID analysis using mesitylene as internal standard.
## Table S2. Screening of solvents

| entry | solvent     | conversion [%] | yield 4a [%] | yield 2a-Si [%] (d.r.) |
|-------|-------------|----------------|--------------|------------------------|
| 1     | 1,4-dioxane | 90             | 30           | 60 (77:23)             |
| 2     | DCE         | 100            | 85           | 15 (50:50)             |
| 3     | toluene     | 60             | 51           | traces                 |
| 4     | CHCl₃       | traces         | traces       | 0                      |
| 5     | MTBE        | 100            | 0            | 99 (81:19)             |
| 6     | THF         | 86             | 32           | traces                 |
| 7     | PhCF₃       | 99             | 87           | 12 (68:32)             |
| 8     | cyclohexane | 100            | traces       | 98 (83:17)             |
| 9     | n-heptane   | 100            | traces       | 96 (81:19)             |
| 10    | EtOH        | 32             | traces       | 24 (75:25)             |
| 11    | TFE         | 100            | traces       | 95 (77:23)             |
| 12    | AcOH        | 100            | 0            | 99 (n.d.)              |
| 13    | NEt₃        | no conv.       | 0            | 0                      |

Reaction conditions: 1a (0.1 mmol, 1.0 equiv.), solvent (1.0 mL, 0.1 M). TBS-protection after hydrogenation. Conversion of \( p \)-cresol. Yields and d.r. values (trans/cis) determined by GC-FID analysis using mesitylene as internal standard. \([a]\) 2 mol% catalyst loading.
**Table S3.** Screening of catalyst loading.

| entry | catalyst loading | conversion [%] | yield 4a [%] | yield 2a-Si [%] (d.r.) |
|-------|------------------|----------------|--------------|-----------------------|
| 1     | 10 mol%          | 100            | 0            | 99 (81:19)           |
| 2     | 2 mol%           | 100            | 0            | 99 (81:19)           |
| 3     | 1 mol%           | 100            | 50           | 50 (75:25)           |

Reaction conditions: 1a (0.1 mmol, 1.0 equiv.), solvent (1.0 mL, 0.1 M). TBS-protection after hydrogenation. Conversion of p-cresol. Yields and d.r. values (trans/cis) determined by GC-FID analysis using mesitylene as internal standard.
**Table S4.** Screening of additional catalyst supports.

| entry | support | conversion [%] | yield 4a [%] | yield 2a-Si [%] (d.r.) |
|-------|---------|----------------|--------------|------------------------|
| 1     | SiO₂ (50 mg) | 100 | traces | 97 (84:16) |
| 2     | neutral Al₂O₃ (50 mg) | 100 | traces | 98 (81:19) |
| 3     | basic Al₂O₃ (50 mg) | 100 | 0 | 99 (80:20) |
| 4     | acidic Al₂O₃ (50 mg) | 100 | 0 | 99 (80:20) |
| 5     | crushed 4Å MS (50 mg) | 100 | 0 | 99 (79:21) |
| 6     | 4Å MS (50 mg) | 99 | traces | 98 (74:26) |
| 7     | TiO₂ (25 mg) | 100 | traces | 97 (79:21) |
| 8     | SiO₂ (25 mg) | 100 | traces | 98 (80:20) |
| 9     | SiO₂ (100 mg) | 100 | 11 | 89 (80:20) |
| 10ᵃ | AcOH | 100 | 66 | 34 (68:32) |

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Reaction conditions: 1a (0.1 mmol, 1.0 equiv.), solvent (1.0 mL, 0.1 M). TBS-protection after hydrogenation. Conversion of p-cresol. Yields and d.r. values (*trans/cis*) determined by GC-FID analysis using mesitylene as internal standard. ³AcOH (1 Vol%) was added.
Table S5. Screening of temperature.

| entry | temperature | conversion [%] | yield 4a [%] | yield 2a-Si [%] (d.r.) |
|-------|-------------|----------------|--------------|------------------------|
| 1     | 40 °C       | 99             | 38           | 61 (80:20)             |
| 2     | 50 °C       | 100            | 0            | 99 (77:23)             |
| 3     | 80 °C       | 100            | 0            | 99 (77:23)             |

Reaction conditions: 1a (0.1 mmol, 1.0 equiv.), solvent (1.0 mL, 0.1 M). TBS-protection after hydrogenation. Conversion of p-cresol. Yields and d.r. values (trans/cis) determined by GC-FID analysis using mesitylene as internal standard.
Table S6. Screening of hydrogen pressure.

| entry | H₂ (bar) | conversion [%] | yield 4d [%] | yield 2d [%] (d.r.) |
|-------|---------|----------------|--------------|---------------------|
| 1     | 5       | 100            | traces       | 98 (88:12)          |
| 2     | 3       | 100            | 16           | 84 (86:14)          |
| 3ᵃ     | 5       | 100            | traces       | 99 (88:12)          |

Reaction conditions: 1d (0.4 mmol, 1.0 equiv.), solvent (1.0 mL, 0.4 M). Yields and d.r. values (trans/cis) determined by GC-FID analysis using mesitylene as internal standard. ³ᵃ 5 wt% Pd/Al₂O₃ without additional neutral Al₂O₃ at 80 °C.

Due to significant amounts of insoluble solids in the process of up-scaling (0.4 mmol) when employing 0.5 wt% Pd/Al₂O₃ (2 mol%) and additional neutral alumina (>200 mg in 1.0 mL solvent), the reproducibility of the reaction was low. Therefore, we decided to reduce the quantities of solids, which restored reproducibility and diastereoselectivity.
Table S7. Screening of other metal-supported heterogeneous catalysts.

| entry | catalyst (5 mol%) | conv. of SM [%] | yield 4d [%] | yield 2d [%] (d.r.) |
|-------|-------------------|-----------------|--------------|--------------------|
| 1     | 5 wt% Ru/Al₂O₃    | 100             | -            | 87 (60:40)         |
| 2     | 5 wt% Ru/AC       | 100             | -            | 89 (65:35)         |
| 3     | 5 wt% Pt/Al₂O₃    | 100             | -            | 78 (80:20)         |
| 4     | 5 wt% Rh/AC       | 100             | -            | 92 (10:90)         |

Reaction conditions: 1d (0.1 mmol, 1.0 equiv.), solvent (1.0 mL, 0.1 M). Yields and d.r. values (trans/cis) determined by GC-FID analysis using mesitylene as internal standard. AC = activated carbon.
**Table S8. Reproducibility of the reaction with Pd/Al₂O₃ from different suppliers.**

| entry | catalyst | supplier         | conv. of SM [%] | yield 2d [%] (d.r.) |
|-------|----------|------------------|------------------|---------------------|
| 1      | 5 wt% Pd/Al₂O₃ | Johnson Matthey | 100              | 92 (88:12)          |
| 2      | 5 wt% Pd/Al₂O₃ | Acros Organics  | 100              | 87 (88:12)          |
| 3      | 5 wt% Pd/Al₂O₃ | ABCR             | 4[b]             | -                   |
| 4      | reduced, dry (Eschat 1241) | ABCR | 100              | 98 (88:12)          |
| 5      | reduced, dry (Eschat 1241) | ABCR | 100              | 98 (86:14)          |
| 6      | 0.5 wt% Pd/Al₂O₃ | ABCR           | 100              | 70 (84:16)          |

Reaction conditions: **1d** (0.1 mmol, 1.0 equiv.), solvent (1.0 mL, 0.1 M). Yields and d.r. values (*trans/cis*) determined by GC-FID analysis using mesitylene as internal standard. [a] Standard catalyst, see “Materials and Methods” section for more details. [b] 4-tBu-cyclohexanone was observed.
4. Synthesis of trans-configurated Cyclohexanols

*General procedure A for the trans-selective hydrogenation of phenols*

A 4 mL screw-cap glass vial, equipped with a magnetic stirring bar, was charged with 5 wt% Pd/Al₂O₃ (2-4 mol%) and solid substrates (0.4 mmol, 1.0 equiv.) as indicated. Solvent (1.0 mL, 0.4 M) and liquid substrates were added. The prepared glass vial was placed in a 150 mL stainless steel autoclave under air. The autoclave was pressurized and depressurized with hydrogen gas three times before the indicated pressure was set. The reaction mixture was stirred at 80 °C for 24 h. After the autoclave was carefully depressurized, the crude mixture was purified by column chromatography on silica gel.

2a, colorless oil, procedure A: 2 mol% catalyst loading, 5 bar H₂, solvent: n-heptane (0.4 M, 1.0 mL). Purification with 20% to 30% Et₂O in pentane. 90% total yield, 80:20 d.r. (determined by ¹H NMR) The major diastereomer was isolated and characterized (74% yield). The hydroxy group occupies the equatorial position based on the ³J coupling between H₄ & H₅. The ⁵J coupling between H₅C₄ & H₅C₂ could not be determined due to overlapping multiplets.

¹H NMR (400 MHz, CDCl₃) δ 3.54 (tt, ³J₆₈,₈ = 10.9 Hz, ³J₆₈,₆ = 4.3 Hz, 1H, H₈C₁), 1.99 – 1.87 (m, 2H), 1.76 – 1.65 (m, 2H), 1.59 (bs, 1H, HO), 1.43 – 1.17 (m, 3H), 1.05 – 0.91 (m, 2H), 8.88 (d, ³J₇₉ = 6.6 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 67.1, 32.4, 31.3, 29.1, 21.8;

ESI-MS calculated [C₇H₁₄O+Na]+ 137.0937, found: 137.0921.

Analytical data are in good accordance with those previously reported for this compound.¹

2ac, colorless oil, procedure A: 4 mol% catalyst loading, 10 bar H₂, solvent: n-heptane (0.4 M, 1.0 mL). Purification with 10% to 20% Et₂O in pentane. 82% total
yield, 55:45 d.r. determined by $^1$H NMR. The major diastereomer was isolated and characterized (44% yield).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.11 (m, 1H, H$_1$), 1.99 – 1.89 (m, 1H), 1.82 – 1.66 (m, 4H), 1.65 – 1.54 (m, 1H), 1.34 – 1.12 (m, 4H), 1.00 (d, $^3$J$_{HH}$ = 6.5 Hz, 3H);

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 76.7, 40.4, 35.6, 33.8, 25.8, 25.3, 18.7;

ESI-MS calculated [C$_7$H$_{14}$O$+$Na]$^+$ 137.093, found: 137.0923.

Analytical data are in good accordance with those previously reported for this compound.

$^1$H NMR (599 MHz, CDCl$_3$) $\delta$ 3.54 (tt, $^3$J$_{ax,ax}$ = 10.9 Hz, $^3$J$_{ax,eq}$ = 4.3 Hz, 1H, H$_{ax}$C$_1$), 2.00 – 1.92 (m, 2H, H$_2$C$_2$), 1.77 (dm, $^2$J$_{HH}$ = 13.0 Hz, 2H, H$_{eq}$C$_3$), 1.50 (bs, 1H, H$_O$), 1.28 – 1.19 (m, 2H, H$_2$C$_2$), 1.19 (q, $^3$J$_{HH}$ = 7.1 Hz, 2H, H$_2$C$_5$), 1.09 (tm, $^3$J$_{ax,ax}$ = 11.5 Hz, 1H, H$_{ax}$C$_4$), 0.94 (ddd, $^2$J$_{HH}$ = 13.4 Hz, $^3$J$_{ax,ax}$ = 11.0 Hz, $^3$J$_{ax,eq}$ = 2.6 Hz, 2H, H$_{ax}$C$_3$), 0.87 (t, $^3$J$_{HH}$ = 7.5 Hz, 3H, H$_3$C$_6$);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 71.4 (C1), 38.6 (C4), 35.8 (C2), 31.0 (C3), 29.4 (C5), 11.8 (C6);

ESI-MS calculated [C$_8$H$_{16}$O$+$Na]$^+$: 151.1093, found: 151.1093;

IR $\tilde{v}$ = 3317, 2925, 2854, 1463, 1449, 1369, 1091, 1052, 1009, 964, 897, 862;

Analytical data are in good accordance with those previously reported for this compound.

GC-FID (prior to purification): Pd-catalyzed (trans)
Rh-catalyzed (cis) 2c, colorless oil, 2 mol% catalyst loading, 5 bar H₂, solvent: n-heptane (0.4 M, 1.0 mL). Purification with 10% to 20% EtOAc in pentane. 88% total yield, 87:13 d.r. determined by GC-MS. The major diastereomer was isolated and characterized (73% yield). The hydroxy group occupies the equatorial position based on the 3\(^{J_{ax,eq}}\) coupling between H\(_{ax}C1\) & H\(_{eq}C2\). The J coupling between H\(_{ax}C4\) & H\(_{ax}C3\) could not be determined due to overlapping multiplets in several solvents (CDCl₃, C₆D₆, CD₃OD). Based on the confirmed trans-configuration for similar substrates with ethyl or tert-butyl groups and the bulkiness of iso-propyl compared to a hydroxy group, it seems very likely that the iso-propyl group occupies the equatorial position and the reported product is indeed the trans-diastereomer.

\(^1\)H NMR (599 MHz, CDCl₃) \(\delta\) 3.51 (tt, 3\(^{J_{ax,ax}}\) = 10.9 Hz, 3\(^{J_{ax,eq}}\) = 4.4 Hz, 1H, H\(_{ax}C1\)) 2.02 – 1.93 (m, 2H, H\(_{eq}C2\)), 1.75 – 1.68 (m, 2H, H\(_2C3\)), 1.59 (bs, 1H, HO), 1.41 (m, 1H, HC5), 1.21
(ddm, $^2J_{HH} =$ 12.0 Hz, $^3J_{ax,ax} =$ 10.7 Hz, 2H, $H_{ax}C2$), $1.05 - 0.97$ (m, 3H, $HC4$, $H_2C3$), 0.84 (d, $^3J_{HH} =$ 6.8 Hz, 6H, $H_2C6$);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 71.4 (C1), 43.2 (C4), 35.9 (C2), 32.5 (C5), 28.0 (C3), 20.1 (C6);

ESI-MS calculated [C$_9$H$_{18}$O+Na]$^+$: 165.1250, found: 165.1251;

IR $\tilde{\nu} =$ 3333, 2928, 2857, 1464, 1450, 1385, 1368, 1086, 1053, 991, 941, 897;

GC-MS (prior to purification):

Pd-catalyzed (trans)

Rh-catalyzed (cis)
2d, white solid, procedure A: 2 mol% catalyst loading, 5 bar H₂, solvent: n-heptane (0.4 M, 1.0 mL). Purification with 10% to 20% EtOAc in pentane. 90% total yield, 87:13 d.r. determined by GC-MS. The major diastereomer was isolated and characterized (75% yield). The trans-configuration was determined based on the 3J_{ax,ax} couplings between H_{ax}C1 & H_{ax}C2, and H_{ax}C4 & H_{ax}C3.

1H NMR (599 MHz, CDCl₃) δ 3.51 (tt, 3J_{ax,ax} = 11.0 Hz, 3J_{ax,eq} = 4.4 Hz, 1H, H_{ax}C1), 2.04 – 1.97 (m, 2H, H_{2eq}C2), 1.81 – 1.74 (m, 2H, H_{2eq}C3), 1.46 (bs, 1H, OH), 1.26 – 1.17 (m, 2H, H_{2ax}C2), 1.09 – 1.00 (m, 2H, H_{2ax}C3), 0.96 (tt, 3J_{ax,ax} = 11.8 Hz, 3J_{ax,eq} = 3.1 Hz, 1H, H_{ax}C4), 0.84 (s, 9H, H₃C6);

13C NMR (151 MHz, CDCl₃) δ 71.4 (C1), 47.3 (C4), 36.2 (C2), 32.4 (C5), 27.8 (C6), 25.8 (C3);

ESI-MS calculated [C₁₀H₂₀O+Na]⁺ 179.1406, found: 179.1403;

IR ν = 3323, 2928, 2858, 1465, 1448, 1363, 1066, 1054, 1037, 981, 900;

Analytical data are in good accordance with those previously reported for this compound.

GC-MS (prior to purification):

Pd-catalyzed (trans)

Rh-catalyzed (cis)
2e, white solid, 2 mol% catalyst loading, 5 bar H₂, solvent: n-heptane (0.4 M, 1.0 mL). Purification with 10% to 20% EtOAc in pentane. 99% total yield, 91:9 d.r. determined by GC-MS. The major diastereomer was isolated and characterized (91% yield). The hydroxy group occupies the equatorial position based on the 3J_{ax,ax} coupling between H_{ax}C1 & H_{ax}C2. The J coupling between H_{ax}C4 & H_{ax}C3 could not be determined due to overlapping multiplets in several solvents (CDCl₃, C₆D₆, CD₃OD). Based on the confirmed trans-configuration for similar substrates with ethyl or tert-butyl groups and the bulkiness of tert-amyl compared to a hydroxy group, it seems very likely that the tert-amyl group occupies the equatorial position and the reported product is indeed the trans-diastereomer.

^1H NMR (599 MHz, CDCl₃) δ 3.49 (tt, 3J_{ax,ax} = 11.0 Hz, 3J_{ax,eq} = 4.4 Hz, 1H, H_{ax}C1), 2.02 – 1.95 (m, 2H, H₂C2), 1.74 (bs, 1H, HO), 1.73 – 1.66 (m, 2H, H₂C3), 1.23 (q, 3J_{HH} = 7.5 Hz, 2H, H₂C7), 1.19 (m, 2H, H₂C2), 1.09 – 0.98 (m, 3H, H_{ax}C3, HC₄), 0.77 (t, 3J_{HH} = 7.6 Hz, 3H, H₃C8), 0.76 (s, 6H, H₃C6);

^13C NMR (151 MHz, CDCl₃) δ 71.3 (C1), 44.5 (C4), 36.3 (C2), 34.7 (C5), 32.9 (C7), 25.3 (C3), 24.4 (C6), 8.2 (C8);

ESI-MS calculated [C_{11}H_{22}O+Na]^+: 193.1563, found: 193.1570;

IR ṽ = 3300, 2930, 2861, 1451, 1379, 1364, 1121, 1069, 980, 899;
GC-MS (prior to purification):

Pd-catalyzed (trans)

Rh-catalyzed (cis)

$2f$, white solid, 4 mol% catalyst loading, 10 bar H$_2$, solvent: $n$-heptane (0.4 M, 1.0 mL), 48 h. Purification with 50% EtOAc in pentane. 84% total yield, 80:20 d.r. determined by GC-MS. The major diastereomer was isolated and characterized (47% yield). The trans-configuration
was determined based on the $^3J_{\text{ax,ax}}$ couplings between $H_{\text{ax}C1}$ & $H_{\text{ax}C2}$, and $H_{\text{ax}C4}$ & $H_{\text{ax}C3}$. The trans-configuration was confirmed by a crystal structure.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.37 (bs, 1H, $H_{\text{N}}$), 3.59 (tt, $^3J_{\text{ax,ax}} = 10.5$ Hz, $^3J_{\text{ax,eq}} = 4.0$ Hz, 1H, $H_{\text{ax}C1}$), 3.39 (tm, $^3J_{\text{ax,ax}} = 11.6$ Hz, 1H, $H_{\text{ax}C4}$), 2.12 – 1.88 (m, 4H, $H_2C2$, $H_2C3$), 1.63 (bs, 1H, $H_{\text{O}}$), 1.43 (s, 9H, $H_3C7$), 1.41 – 1.28 (m, 2H, $H_2C2$), 1.26 – 1.05 (m, 2H, $H_2C3$);

$^1$H NMR (599 MHz, CDCl$_3$) $\delta$ 4.35 (bs, 1H, $H_{\text{N}}$), 3.57 (tt, $^3J_{\text{ax,ax}} = 10.6$ Hz, $^3J_{\text{ax,eq}} = 4.2$ Hz, 1H, $H_{\text{ax}C1}$), 3.40 (bs, 1H, $H_{\text{ax}C4}$), 2.04 – 1.91 (m, 4H, $H_2C2$, $H_2C3$), 1.54 (s, 1H, $H_{\text{O}}$), 1.42 (s, 9H, $H_3C7$), 1.35 (dm, $^2J_{\text{HH}} = 13.2$ Hz, 2H, $H_2C2$), 1.14 (ddm, $^2J_{\text{HH}} = 12.5$ Hz, $^3J_{\text{ax,ax}} = 11.1$ Hz, 2H, $H_2C3$);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 155.4 (C5), 79.4 (C6), 69.9 (C1), 49.0 (C4), 34.1 (C2), 31.3 (C3), 28.5 (C7);

ESI-MS calculated [C$_{11}$H$_{21}$NO$_3$+Na]$^+$: 238.1414, found: 238.1429;

IR $\tilde{\nu}$ = 3342, 2935, 2856, 1680, 1653, 1559, 1533, 1363, 1314, 1230, 1171, 1069, 951, 891;

Analytical data are in good accordance with those previously reported for this compound.²

GC-MS (prior to purification):

Pd-catalyzed (trans)

![Graph]

| peak | R.T. | first | max | last | PK | peak | corr. | corr. | % of | total |
|------|------|-------|-----|------|----|------|-------|-------|------|-------|
| # min scan scan scan | TY | height | area | % max. |   |
| 1 | 26.146 | 3753 | 3764 | 3777 | H2 | 136145 | 3885491 | 24.46% | 19.655% |
| 2 | 26.367 | 3778 | 3791 | 3919 | H | 455635 | 15882568 | 100.00% | 80.345% |

Rh-catalyzed (cis)
S21

2f, white solid, procedure A: starting from 4-aminophenol, 4 mol% catalyst loading, 10 bar H₂, solvent: iso-propanol (0.2 M, 2.0 mL), additive: K₂CO₃ (0.2 equiv.) Addition of K₂CO₃ increased the reactivity. Boc-protection prior to isolation by addition of NEt₃ (3.0 equiv.) and Boc₂O (3.0 equiv.). Purification with 40% to 50% EtOAc in pentane. 78% total yield, 88:12 d.r. determined by GC-MS. The major diastereomer was isolated and characterized (54% yield).

Analytical data are in accordance with compound 2f.

GC-MS (prior to purification):

Pd-catalyzed (trans)
**2f**, white solid, procedure A: starting from 4-nitrophenol, 4 mol% catalyst loading, 10 bar H₂, solvent: *iso*-propanol (0.2 M, 2.0 mL), additive: K₂CO₃ (0.2 equiv.) Addition of K₂CO₃ increased the reactivity. Boc-protection prior to isolation by addition of NEt₃ (3.0 equiv.) and Boc₂O (3.0 equiv.). Purification with 40% to 50% EtOAc in pentane. 80% total yield, 89:11 d.r. determined by GC-MS. The major diastereomer was isolated and characterized (51% yield).

Analytical data are in accordance with compound **2f**.

**GC-MS** (prior to purification):

Pd-catalyzed (**trans**) 2g, off-white solid, procedure A: 4 mol% catalyst loading, 10 bar H₂, solvent: *n*-heptane (0.4 M, 1.0 mL), 48 h. Purification with 40% to 50% EtOAc in pentane. 93% total yield, 77:23 d.r. determined by GC-MS. The major diastereomer was isolated and characterized (43% yield). The **trans**-configuration was determined based on the ³Jₐₓ,ₐₓ couplings between HₐₓC1 & HₐₓC2, and HₐₓC4 & HₐₓC3. Determination of ³Jₐₓ,ₐₓ coupling between HₐₓC4 & HₐₓC3 and J couplings assigned to HₐₓC2 and HₐₓC3 were possible with homonuclear decoupling experiments by irradiation at H₂C5.
$^1$H NMR (599 MHz, CDCl$_3$) $\delta$ 4.58 (bs, 1H, HN), 3.54 (tt, $^3$$J_{ax,ax}$ = 10.9 Hz, $^3$$J_{ax,eq}$ = 4.3 Hz, 1H, $H_{ax}$C1), 2.96 (t, $^3$$J_{HH}$ = 6.5 Hz, 2H, $H_2$C5), 2.02 – 1.91 (m, 2H, $H_{eq}$C2), 1.77 (ddm, $^2$$J_{HH}$ = 13.4 Hz, $^3$$J_{eq,ax}$ = 4.3 Hz, 2H, $H_{eq}$C3), 1.54 (bs, 1H, HO), 1.43 (s, 9H, HC8), 1.41 – 1.33 (tm, $^3$$J_{ax,ax}$ = 11.6 Hz, 1H, $H_{ax}$C4), 1.24 (tdd, $^2$$J_{HH}$ = 12.5 Hz, $^3$$J_{ax,ax}$ = 10.8 Hz, $^3$$J_{ax,eq}$ = 3.5 Hz, 2H, $H_{ax}$C2), 1.03 – 0.93 (tdd, $^2$$J_{HH}$ = 13.7 Hz, $^3$$J_{ax,ax}$ = 11.5 Hz, $^3$$J_{ax,eq}$ = 3.4 Hz, 2H, $H_{ax}$C3);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 155.0 (C6), 78.9 (C7), 70.2 (C1), 47.8 (C5), 37.6 (C4), 33.9 (C2), 29.4 (C3), 28.0 (C8);

ESI-MS calculated [C$_{12}$H$_{23}$NO$_3$+Na]$^+$: 252.1570, found: 252.1574;

IR $\tilde{\nu}$ = 3335, 2978, 2928, 2857, 1686, 1522, 1452, 1366, 1273, 1248, 1169, 1045, 1013, 731;

GC-MS (prior to purification):

Pd-catalyzed (trans)

| peak | R.T. | first max last | PK | peak | corr. | corr. | % of total |
|------|------|----------------|----|------|-------|-------|-----------|
|     |      | min | scan | scan | scan | TY | height | area | % max. | total |
| 1   | 28.733 | 4186 | 4295 | 4211 | BU | 2 | 29907 | 801701 | 30.15% | 23.163% |
| 2   | 28.818 | 4211 | 4220 | 4232 | UU | 3 | 94623 | 2659371 | 100.00% | 76.837% |

Rh-catalyzed (cis)
2h, colorless oil, 3 mol% catalyst loading, 5 bar H₂, solvent: n-heptane (0.4 M, 1.0 mL). Purification with 30% EtOAc in pentane. 99% total yield, 56:44 d.r. determined by ¹H NMR. The major diastereomer was isolated and characterized (38% yield). The hydroxy group occupies the equatorial position based on the ³Jax,ax coupling between HaxC1 & HaxC2.

¹H NMR (300 MHz, CDCl₃) δ 3.65 (s, 3H), 3.63 – 3.52 (m, 1H), 2.24 (tt, ³Jax,ax = 11.9 Hz, ³Jax,eq = 3.5 Hz, 1H, HaxC1), 2.07 – 1.93 (m, 4H), 1.81 (s, 1H), 1.57 – 1.39 (m, 2H), 1.36 – 1.16 (m, 2H);

³C NMR (75 MHz, CDCl₃) δ 176.2, 69.9, 51.8, 42.2, 34.6, 27.3;

ESI-MS calculated [C₈H₁₄O₃+Na⁺]: 181.0835, found: 181.0842;

Analytical data are in good accordance with those previously reported for this compound.³

2i, colorless oil, 2 mol% catalyst loading, 5 bar H₂, solvent: n-heptane (0.4 M, 1.0 mL). Purification with 20% to 30% EtOAc in pentane. 89% total yield, 76:24 d.r. determined by ¹H NMR. The major diastereomer was isolated and characterized (67% yield). The trans-configuration was determined based on the ³Jax,ax couplings between HaxC1 & HaxC2, and HaxC4 & HaxC3. Determination of ³Jax,ax coupling between HaxC4 & HaxC3 and was possible with homonuclear decoupling experiments by irradiation at H₂C5.

¹H NMR (599 MHz, CDCl₃) δ 4.08 (q, ³JHH = 7.2 Hz, 2H, H₂C7), 3.60 – 3.46 (tm, ³Jax,ax = 10.9 Hz, 1H, HaxC1), 2.14 (d, ³JHH = 7.0, 2H, H₂C7), 2.04 (bs, 1H, HO), 2.01 – 1.89 (m, 2H, H₂C2), 1.80 – 1.71 (m, 2H, H₂C3), 1.73 – 1.65 (tm, ³Jax,ax = 11.5 Hz, 1H, HaxC4), 1.29 – 1.23 (m, 2H, H₂C2), 1.21 (t, ³JHH = 7.1 Hz, 3H, H₃C8), 1.06 – 0.95 (m, 2H, H₂C3);

¹³C NMR (151 MHz, CDCl₃) δ 173.0 (C6), 71.4 (C1), 59.5 (C7), 41.4 (C5), 35.2 (C2), 34.0 (C4), 31.0 (C3), 13.9 (C8);

ESI-MS calculated [C₁₀H₁₈O₃+Na⁺]: 209.1148, found: 209.1161;
Analytical data are in good accordance with those previously reported for this compound.  

2j, colorless oil, 3 mol% catalyst loading, 10 bar H₂, solvent: n-heptane (0.4 M, 1.0 mL). Purification with 20% to 30% EtOAc in pentane. 91% total yield, 78:22 d.r. determined by 

1H NMR. The major diastereomer was isolated and characterized (68% yield). The trans-configuration was determined based on the $^3J_{ax,ax}$ couplings between H$_{ax}$C1 & H$_{ax}$C2, and H$_{ax}$C4 & H$_{ax}$C3. Determination of $^3J_{ax,ax}$ coupling between H$_{ax}$C4 & H$_{ax}$C3 and was possible with homonuclear decoupling experiments by irradiation at H$_2$C5. 

1H NMR (599 MHz, CDCl$_3$) δ 3.64 (s, 3H, H$_3$C8), 3.51 (tt, $^3J_{ax,ax} = 10.9$ Hz, $^3J_{ax,eq} = 4.3$ Hz, 1H, H$_{ax}$C1), 2.32 – 2.26 (m, 2H, H$_2$C6), 1.98 – 1.90 (m, 2H, H$_2$C2), 1.79 (bs, 1H, HO), 1.77 – 1.71 (m, 2H, H$_2$C3), 1.51 (dt, $^3J_{HH} = 8.2$, 7.0 Hz, 2H, H$_2$C5), 1.21 (m, 2H, H$_2$C2). 1.18 (tm, $^3J_{ax,ax} = 12.4$ Hz, 1H, H$_{ax}$C4), 0.99 – 0.89 (m, 2H, H$_2$C3);

13C NMR (151 MHz, CDCl$_3$) δ 174.5 (C7), 71.0 (C1), 51.6 (C8), 36.3 (C4), 35.4 (C2), 32.0 (C6), 31.6 (C5), 31.0 (C3);

ESI-MS calculated [C$_{10}$H$_{18}$O$_3$+Na$^+$]: 209.1148, found: 209.1162; 

IR $\tilde{\nu}$ = 3383, 2928, 2857, 1728, 1452, 1437, 1265, 1169, 1047, 1015, 909, 729, 646.

2k, white solid, 3 mol% catalyst loading, 10 bar H₂, solvent: n-heptane (0.4 M, 1.0 mL). Purification with 10% EtOAc in CH$_2$Cl$_2$. 65% total yield, 78:22 d.r. determined by GC-MS. The major diastereomer was isolated and characterized (33% yield). The trans-configuration was determined based on the $^3J_{ax,ax}$ couplings between H$_{ax}$C1 & H$_{ax}$C2, and H$_{ax}$C4 & H$_{ax}$C3.

1H NMR (599 MHz, CDCl$_3$) δ 3.53 (tt, $^3J_{ax,ax} = 10.2$ Hz, $^3J_{ax,eq} = 4.2$ Hz, 1H, H$_{ax}$C1), 2.00 – 1.93 (m, 2H, H$_2$C2), 1.85 – 1.78 (m, 2H, H$_2$C3), 1.49 (bs, 1H, HO), 1.31 – 1.14 (m, 4H, H$_2$C2, H$_2$C3), 1.21 (s, 12H, H$_3$C6). 0.79 (tt, $^3J_{ax,ax} = 12.2$ Hz, $^3J_{ax,eq} = 3.5$ Hz, 1H, H$_{ax}$C4);
$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 83.1 (C5), 70.9 (C1), 36.2 (C2), 26.9 (C3), 24.4 (C6);  
$^{11}$B NMR (128 MHz, CDCl$_3$) $\delta$ 34.4 (bs);  
ESI-MS calculated [C$_{12}$H$_{23}$BO$_3$+Na]$^+$: 249.1632, found: 249.1640;  
IR $\tilde{\nu}$ = 3306, 2976, 2926, 2852, 1381, 1363, 1319, 1146, 1092, 1059, 961, 862, 848;  
GC-MS (prior to purification):  
Pd-catalyzed (trans)  

| peak # | R.T. | First | max | last | PK | area | % | total |
|-------|------|-------|-----|------|----|------|---|------|
| 1     | 22.949 | 3210  | 3218 | 3235 | M2 | 148996 | 3608228 | 27.76% | 21.725% |
| 2     | 23.253 | 3258  | 3270 | 3322 | M2 | 463486 | 1300059 | 100.00% | 78.275% |

Rh-catalyzed (cis)  

| peak # | R.T. | First | max | last | PK | area | % | total |
|-------|------|-------|-----|------|----|------|---|------|
| 1     | 23.949 | 3371  | 3389 | 3429 | H2 | 1511071 | 40586427 | 100.00% | 76.595% |
| 2     | 24.214 | 3422  | 3434 | 3473 | H2 | 536769 | 14840548 | 30.56% | 23.405% |
2l, white solid, 2 mol% catalyst loading, 5 bar H₂, solvent: n-heptane (0.4 M, 1.0 mL). Purification with 15% EtOAc in pentane. 86% total yield, 85:15 d.r. determined by GC-MS. The major diastereomer was isolated and characterized (65% yield). The trans-configuration was determined based on the $^{3}J_{ax,ax}$ couplings between $H_{ax}C1$ & $H_{ax}C2$, and $H_{ax}C4$ & $H_{ax}C3$.

$^{1}H$ NMR (599 MHz, CDCl₃) $\delta$ 3.50 (tt, $^{3}J_{ax,ax} = 10.7$ Hz, $^{3}J_{ax,eq} = 4.3$ Hz, 1H, $H_{ax}C1$), 2.06 – 1.99 (m, 2H, $H_{2}C2$), 1.79 – 1.72 (m, 2H, $H_{2}C3$), 1.43 (bs, 1H, $HO$), 1.22 – 1.06 (m, 4H, $H_{2}C2$, $H_{2}C3$), 0.44 – 0.38 (tm, $^{3}J_{ax,ax} = 12.4$ Hz, 1H, $H_{ax}C4$), –0.06 (s, 9H, $H_{3}C5$);

$^{13}C$ NMR (151 MHz, CDCl₃) $\delta$ 71.4 (C1), 38.0 (C2), 26.6 (C3), 24.2 (C4), –3.3 (C5);

$^{29}Si$ NMR (119 MHz, CDCl₃) $\delta$ 2.9;

ESI-MS calculated [C₉H₂₀OSi+Na]+: 195.1176, found: 195.1184;

IR $\tilde{\nu}$ = 3271, 2924, 2847, 1445, 1248, 1053, 966, 891, 854, 831, 734, 702, 689;

GC-MS (prior to purification):

Pd-catalyzed (trans)

Rh-catalyzed (cis)
2m, white solid, procedure A: 4 mol% catalyst loading, 10 bar H₂, solvent: iso-propanol (0.2 M, 2.0 mL), additive: K₂CO₃ (0.1 equiv.). Addition of K₂CO₃ increased the reactivity and selectivity. Purification with 10% to 20% EtOAc in pentane. 76% total yield, 90:10 d.r. determined by ¹H NMR. The major diastereomer was isolated and characterized (44% yield). The trans-configuration was determined based on the ³Jax,ax couplings between HaxC1 & HaxC2, and HaxC4 & HaxC3. The trans-configuration was confirmed by a crystal structure.

¹H NMR (599 MHz, CDCl₃) δ 7.32 – 7.28 (m, 2H, Hₐr), 7.22 – 7.18 (m, 3H, Hₐr), 3.69 (tt, ³Jax,ax = 12.1 Hz, ³Jax,eq = 4.4 Hz, 1H, HaxC1), 2.50 (tt, ³Jax,ax = 12.1, ³Jax,eq = 3.5 Hz, 1H, HaxC4), 2.15 – 2.05 (m, 2H, HₐC2), 1.98 – 1.91 (m, 2H, HₐeqC3), 1.60 (bs, 1H, HₐO), 1.55 (ddddd, 2JHH = 13.2 Hz, ³Jax,ax = 11.9 Hz, ³Jax,eq = 3.1 Hz, ³Jax,eq = 3.1 Hz, 2H, HₐC3), 1.49 – 1.39 (m, 2H, H₂C2);

¹³C NMR (151 MHz, CDCl₃) δ 146.7 (Cₐr), 128.5 (Cₐr), 126.9 (Cₐr), 126.2 (Cₐr), 70.8 (C₁), 43.6 (C₄), 36.1 (C₂), 32.6 (C₃).

ESI-MS calculated [C₁₂H₁₆O+Na]⁺: 199.1093, found: 199.1103.

Analytical data are in good accordance with those previously reported for this compound.⁵
oH 2n, off-white solid, procedure A: 4 mol% catalyst loading, 10 bar H₂, solvent: *iso*-propanol (0.2 M, 2.0 mL), additive: K₂CO₃ (0.2 equiv.).

Addition of K₂CO₃ increased the reactivity. Purification with 2% to 5% to 10% MeOH in CH₂Cl₂. 79% total yield, 87:13 d.r. determined by GC-MS. Both diastereomers were isolated and characterized together and the major signals are reported. The hydroxy group occupies the equatorial position based on the $^3J_{ax,ax}$ coupling between $H_{ax}C1$ & $H_{ax}C2$.

$^1$H NMR (400 MHz, CDCl₃) $\delta$ 3.57 (dt, $^3J_{ax,ax} = 9.7$ Hz, $^3J_{ax,eq} = 5.3$ Hz, 1H, $H_{ax}C1$), 3.50 – 3.35 (m, 4H), 2.63 – 2.41 (m, 4H), 2.30 (bs, 1H), 2.09 – 1.96 (m, 2H), 1.94 – 1.80 (m, 2H), 1.76 – 1.50 (m, 2H), 1.45 (s, 9H), 1.37 – 1.20 (m, 3H);

$^{13}$C NMR (101 MHz, CDCl₃) $\delta$ 154.6, 79.8, 70.6, 62.9, 49.2, 49.0, 34.7, 32.0, 28.6, 26.5;

ESI-MS calculated [C₁₅H₂₈N₂O₃+H]⁺: 285.2173, found: 285.2189;

IR $\bar{v}$ = 2930, 2853, 1686, 1404, 1252, 1175, 1119, 1074, 955, 868, 775;

GC-MS (prior to purification):

Pd-catalyzed (trans)

Rh-catalyzed (cis)
2o, white solid, procedure A: 4 mol% catalyst loading, 10 bar H₂, solvent: isopropanol (0.2 M, 2.0 mL). Purification with 40% to 50% EtOAc in pentane. 87% total yield, 67:31:2 d.r. (trans/trans:trans/cis: cis/cis) determined by GC-MS. The major diastereomer was isolated and characterized (54% yield). The trans-configuration was determined based on the $^3J_{ax,ax}$ couplings between H$_{ax}$C1 & H$_{ax}$C2, and H$_{ax}$C4 & H$_{ax}$C3. The multiplets of H$_{ax}$C4 and H$_{ax}$C2 are overlapping. The trans-configuration was confirmed by a crystal structure.

$^1$H NMR (599 MHz, CDCl$_3$) δ 3.52 (tt, $^3J_{ax,ax} = 10.9$ Hz, $^3J_{ax,eq} = 4.4$ Hz, 2H, H$_{ax}$C1), 2.06 – 1.98 (m, 4H, H$_2$C2), 1.74 – 1.67 (m, 4H, H$_{eq}$C3), 1.52 (bs, 2H, HO), 1.28 – 1.22 (tm, $^3J_{ax,ax} = 12.0$ Hz, 2H, H$_{ax}$C4), 1.24 – 1.16 (m, 4H, H$_2$C2), 1.05 (dddd, $^2J_{HH} = 13.1$ Hz, $^3J_{ax,ax} = 11.6$ Hz, $^3J_{ax,eq} = 3.1$ Hz, $^3J_{ax,eq} = 3.1$ Hz, 4H, H$_{ax}$C3), 0.72 (s, 6H, H$_3$C6);

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 71.5 (C1), 43.3 (C4), 36.8 (C5), 36.4 (C2), 25.1 (C3), 20.8 (C6);

ESI-MS calculated [C$_{15}$H$_{28}$O$_2$+Na]$^+$: 263.1982, found: 263.1978;

IR $\tilde{\nu} = 3342, 2982, 1734, 1373, 1238, 1045, 914, 731, 648, 633, 608$.

GC-MS (prior to purification):

Pd-catalyzed (trans)
Rh-catalyzed (cis)

2p, white solid, procedure A: 4 mol% catalyst loading, 10 bar H2, solvent: iso-propanol (0.2 M, 2.0 mL). Purification with 40% to 50% EtOAc in pentane. 72% total yield, 90:10 d.r. determined by GC-MS. Both diastereomers were isolated and characterized together. The signals of the major diastereomer are reported.

1H NMR (400 MHz, CDCl3) δ 4.07 (m, 1H), 3.63 (m, 1H), 2.08 – 1.95 (m, 2H), 1.86 – 1.36 (m, 15H), 1.24 (m, 4H), 1.16 – 0.97 (m, 2H), 0.95 – 0.80 (m, 2H), 0.72 (s, 3H);

13C NMR (101 MHz, CDCl3) δ 82.1, 67.4, 51.1, 48.0, 43.6, 41.5, 38.7, 37.2, 37.0, 34.9, 33.7, 32.3, 30.7, 28.9, 25.9, 23.4, 15.8, 11.2;
ESI-MS calculated $[\text{C}_{18}\text{H}_{30}\text{O}_{2}\text{Na}]^+$: 301.2138, found: 301.2149;
IR $\tilde{\nu} = 3376, 2915, 2847, 1717, 1653, 1449, 1373, 1265, 1063, 1051, 1026, 955, 582$;
GC-MS (prior to purification):
Pd-catalyzed ($trans$)

| peak | R.T. | first | max | last | PK | peak | corr. | corr. | % of | % max. | total |
|------|------|-------|-----|------|----|------|-------|-------|------|--------|-------|
|      |      |       |     |      |    |      |       |       |      |        |       |
| 1    | 41.24 | 6305  | 6340| 6359 | BU | 7    | 82382 | 2761245 | 11.38% | 10.214% |       |
| 2    | 41.55 | 6376  | 6393| 6421 | BU | 2    | 735745| 23744400| 100.00%| 89.786% |       |

Rh-catalyzed ($cis$)

| peak | R.T. | first | max | last | PK | peak | corr. | corr. | % of | % max. | total |
|------|------|-------|-----|------|----|------|-------|-------|------|--------|-------|
|      |      |       |     |      |    |      |       |       |      |        |       |
| 1    | 41.51 | 6370  | 6386| 6434 | PU | 2    | 1698318| 66695306 | 100.00%| 89.54% |       |
| 2    | 41.85 | 6434  | 6444| 6480 | UU | 8    | 166707 | 7791858 | 11.68% | 10.46% |       |
2q, white solid, procedure A: 4 mol% catalyst loading, 10 bar H₂, solvent: iso-propanol (0.4 M, 1.0 mL). Boc-protection prior to isolation by addition of NEt₃ (3.0 equiv.) and Boc₂O (3.0 equiv.). Purification with 20% to 30% EtOAc in pentane. 95% total yield, 87:13 d.r. determined by GC-MS. The major diastereomer was isolated and characterized (72% yield). The trans-configuration was determined based on the $^3J_{eq,ax}$ couplings between $H_{eq}C1$ & $H_{ax}C2$, and $H_{eq}C4$ & $H_{ax}C3$. Determination of $^3J_{eq,ax}$ coupling between $H_{eq}C4$ & $H_{ax}C5$ was possible with homonuclear decoupling experiments by irradiation at $H_3C10$. Hydroxy and methyl group occupy the corresponding axial position. The trans-configuration was confirmed by a crystal structure.

$^1$H NMR (599 MHz, CDCl₃) δ 4.41 – 4.35 (dm, $^3J_{eq,ax} = 5.7$ Hz, 1H, $H_{eq}C4$), 3.96 (ddm, $^2J_{HH} = 14.3$ Hz, $^3J_{eq,eq} = 2.6$ Hz, 1H, $H_{eq}C2$), 3.90 (m, 1H, $H_{eq}C1$), 3.04 – 2.98 (m, 1H, $H_{ax}C2$), 2.06 (dm, $^2J_{HH} = 13.8$ Hz, 1H, $H_2C5$), 1.79 – 1.70 (m, 1H, $H_2C6$), 1.70 – 1.63 (m, 1H, $H_2C6$), 1.45 (s, 9H, $H_3C9$), 1.27 (dm, $^2J_{HH} = 13.8$ Hz, 1H, $H_2C5$), 1.24 (s, 1H, HO), 1.12 (d, $^3J_{HH} = 6.9$ Hz, 3H, $H_3C10$);

$^{13}$C NMR (151 MHz, CDCl₃) δ 156.1 (C7), 79.7 (C8), 64.8 (C1), 46.2 (C4), 44.7 (C2), 28.6 (C9), 25.4 (C6), 23.9 (C5), 15.4 (C10);

ESI-MS calculated [C_{11}H_{21}NO_3+Na]^+ 238.1414, found: 238.1435;

IR $\tilde{v} = 3449, 2967, 2895, 1651, 1422, 1362, 1335, 1248, 1153, 1090, 1034, 1018, 874, 831, 766, 638$;

GC-MS (prior to purification):

Pd-catalyzed (trans)
Rh-catalyzed (cis)

2r, colorless oil, procedure A: 4 mol% catalyst loading, 10 bar H2, solvent: iso-propanol (0.4 M, 1.0 mL). Boc-protection prior to isolation by addition of NEt3 (3.0 equiv.) and Boc2O (3.0 equiv.). Purification with 10% to 30% EtOAc in pentane. 62% total yield, 73:27 d.r. determined by GC-MS. The major diastereomer was isolated and characterized (47% yield).

The title compound exists as a mixture of multiple rotamers.

1H NMR (400 MHz, CDCl3) δ 4.70 (m, 1H), 4.28 – 3.93 (m, 3H), 3.61 (s, 1H), 2.69 (dt, J = 41.8, 11.4 Hz, 1H), 2.42 – 2.14 (m, 2H), 2.02 – 1.89 (m, 1H), 1.79 – 1.60 (m, 1H), 1.51 – 1.35 (m, 9H), 1.32 – 1.12 (m, 4H);

13C NMR (101 MHz, CDCl3) δ 171.6, 171.5, 155.6, 155.3, 80.6, 66.8, 66.6, 61.4, 54.1, 52.9, 48.6, 47.7, 30.6, 30.0, 29.8, 28.6, 28.4, 25.1, 24.9, 23.8, 21.9, 21.9, 14.4;

ESI-MS calculated [C13H23NO5+Na]+ 296.1468, found: 296.1479;

IR ν = 2978, 2362, 1734, 1696, 1684, 1395, 1368, 1340, 1240, 1146, 1072, 1022, 978, 874;

Analytical data are in good accordance with those previously reported for this compound.

GC-MS (prior to purification):

Pd-catalyzed (trans)
2s, white solid, procedure A: 4 mol% catalyst loading, 10 bar H₂, solvent: iso-propanol (0.2 M, 2.0 mL). Boc-protection prior to isolation by addition of NEt₃ (1.5 equiv.) and Boc₂O (1.5 equiv.). Purification with 20% to 30% EtOAc in pentane. 75% total yield, 67:33 d.r. determined by GC-MS. The major diastereomer was isolated and characterized (40% yield).

The trans-configuration was determined based on the ³Jₑ𝑞,ₐₓ couplings between Hₑ𝑞C₁ & Hₑ𝑞C₂, and Hₑ𝑞C₄ & Hₑ𝑞C₅. Hydroxy and phenyl group occupy the corresponding axial positions.

¹H NMR (599 MHz, CDCl₃) δ 7.37 – 7.33 (m, 2H, HₑqC₁₂, HₑqC₁₃), 7.27 – 7.20 (m, 3H, HₑqC₁₁, HₑqC₁₀), 5.44 (d, ³Jₑ𝑞,ₐₓ = 4.7 Hz, 1H, HₑqC₄), 4.09 (dd, ²Jₕₕ = 14.6 Hz, ³Jₑq,ₑq = 2.7 Hz, 1H, HₑqC₂), 3.87 (dm, ³Jₑ𝑞,ₐₓ = 2.8 Hz, 1H, HₑqC₁), 2.91 (dd, ²Jₕₕ = 14.4 Hz, ³Jₑq,ₑq = 1.9 Hz, 1H, HₑqC₂), 2.34 (dm, ²Jₕₕ = 13.9 Hz, 1H, HₑqC₅), 2.12 (dm, ²Jₕₕ = 14.4 Hz, 1H, HₑqC₅), 2.00 (bs, 1H, Hₒ), 1.75 – 1.68 (m, 1H, HₑqC₆), 1.63 (dm, ²Jₕₕ = 13.9 Hz, 1H, HₑqC₆), 1.48 (s, 9H, H₃C₉);

¹³C NMR (151 MHz, CDCl₃) δ 156.8 (C₈), 139.5 (C₁₀), 128.8, 126.8, 126.5, 80.3 (C₈), 65.0 (C₁), 53.4 (C₄), 46.0 (C₂), 28.6 (C₉), 26.4 (C₆), 21.7 (C₅);

ESI-MS calculated [(C₁₆H₂₃NO₃)₂+Na]⁺ 577.3248, found: 577.3262;
Analytical data are in good accordance with those previously reported for this compound.⁷

GC-MS (prior to purification):
Pd-catalyzed (trans)
2t, yellow oil, procedure A: 4 mol% catalyst loading, 10 bar H₂, solvent: iso-propanol (0.4 M, 1.0 mL). Boc-protection prior to isolation by addition of NEt₃ (3.0 equiv.) and Boc₂O (3.0 equiv.). Purification with 10% to 30% EtOAc in pentane. 91% total yield, 93:7 d.r. determined by GC-MS. The major diastereomer was isolated and characterized (78% yield). The trans-configuration was determined based on the 3J_{ax,ax} couplings between H_{ax}C1 & H_{ax}C2, and H_{ax}C3 & H_{ax}C2.

1H NMR (599 MHz, CDCl₃) δ 363 (tt, 2J_{HH} = 11.0 Hz, 3J_{eq,ax} = 4.4 Hz, 1H, H_{ax}C1), 3.52 (ddd, 2J_{HH} = 13.7 Hz, 3J_{eq,ax} = 6.1 Hz, 3J_{eq,eq} = 3.8 Hz, 1H, H_{eq}C7), 2.98 (td, 3J_{ax,ax} = 11.3 Hz, 3J_{ax,eq} = 3.2 Hz, 1H, H_{ax}C3), 2.45 – 2.38 (m, 1H, H₂C2), 2.12 (bs, 1H, HO), 2.00 – 1.92 (m, 1H, H₂C6), 1.75 – 1.62 (m, 3H, H₂C8, H₂C5, H_{eq}C9), 1.60 – 1.50 (m, 1H, H₂C8), 1.50 – 1.40 (m, 2H, H₂C2, H₂C4), 1.43 (s, 9H, H₂C12), 1.33 – 1.20 (m, 1H, H₂C6), 1.07 (ddd, 2J_{HH} = 12.9 Hz, 3J_{ax,ax} = 9.0 Hz, 3J_{ax,eq} = 4.0 Hz, 1H, H_{ax}C9), 1.05 – 0.95 (m, 1H, H₂C5);

13C NMR (151 MHz, CDCl₃) δ 155.4 (C10), 79.4 (C11), 69.7 (C1), 59.2 (C3), 40.7 (C2), 39.8 (C7), 37.4 (C4), 35.2 (C6), 29.9 (C5), 28.6 (C12), 27.0 (C9), 22.9 (C8);

ESI-MS calculated [C₁₄H₂₅NO₃+Na]⁺ 278.1727, found: 278.1739;

IR ʋ = 3428, 2972, 2928, 2861, 1686, 1668, 1408, 1364, 1250, 1165, 1146, 1059, 957, 772;
GC-MS (prior to purification):

Pd-catalyzed (*trans*)

| peak | R.T. | first | min | max | last | PK | peak | corr. | corr. | % of total |
|------|------|-------|-----|-----|------|----|------|-------|-------|------------|
| 1    | 30.583 | 4508 | 4521 | 4537 | BB 2 | 222719 | 6821613 | 6.97% | 6.513% |
| 2    | 31.011 | 4573 | 4594 | 4619 | BV 3 | 3116749 | 97922847 | 100.00% | 93.487% |
A 100 mL glass cylinder, equipped with a magnetic stirring bar, was charged with 5 wt% Pd/Al₂O₃ (1.42 g, 0.66 mmol, 2 mol%), \textit{p-}tert-butylphenol (5.00 g, 33.28 mmol, 1.0 equiv.) and \textit{n}-heptane (42.0 mL, 0.8 M). The prepared glass cylinder was placed in a 400 mL stainless steel autoclave under air. The autoclave was pressurized and depressurized with hydrogen gas three times before the hydrogen pressure was set to 10 bar. The reaction mixture was stirred at 80 °C for 21 h. After the autoclave was carefully depressurized, the crude mixture was filtered over a pad of silica gel (eluent: 100% EtOAc) and both diastereomers were isolated together. White solid, 99% total yield (5.18 g, 33.15 mmol), 88:12 d.r. (determined by \textsuperscript{1}H NMR). Characterization data was in accordance with \textit{2d}. 
A 50 mL glass cylinder, equipped with a magnetic stirring bar, was charged with 5 wt% Pd/Al₂O₃ (255 mg, 0.12 mmol, 4 mol%), p-nitrophenol (417 mg, 3.0 mmol, 1.0 equiv.), K₂CO₃ (83 mg, 0.6 mmol, 0.2 equiv.) and iso-propanol (15.0 mL, 0.2 M). The prepared glass cylinder was placed in a 150 mL stainless steel autoclave under air. The autoclave was pressurized and depressurized with hydrogen gas three times before the hydrogen pressure was set to 10 bar. The reaction mixture was stirred at 80 °C for 24 h. After the autoclave was carefully depressurized, the crude mixture was purified by column chromatography on silica gel (40% to 50% EtOAc in pentane). White solid, 87% total yield (559 mg, 2.60 mmol), 90:10 d.r. The major isomer was isolated in 40% yield (257 mg, 1.19 mmol). Characterization data was in accordance with 2f.

Pd-catalyzed (trans)
A 50 mL glass cylinder, equipped with a magnetic stirring bar, was charged with 5 wt% Pd/Al₂O₃ (255 mg, 0.12 mmol, 4 mol%), 5-hydroxy-2-methylpyridine (327 mg, 3.0 mmol, 1.0 equiv.) and iso-propanol (7.5 mL, 0.4 M). The prepared glass cylinder was placed in a 150 mL stainless steel autoclave under air. The autoclave was pressurized and depressurized with hydrogen gas three times before the hydrogen pressure was set to 10 bar. The reaction mixture was stirred at 80 °C for 24 h. After the autoclave was carefully depressurized, the crude mixture was purified by column chromatography on silica gel (20% to 40% EtOAc in pentane). White solid, 95% total yield (613 mg, 2.85 mmol), 86:14 d.r. The major isomer was isolated in 60% yield (390 mg, 1.81 mmol). Characterization data was in accordance with 2q.

**GC-MS (prior to purification):**

Pd-catalyzed (trans)
5. Synthesis of cis-configurated Cyclohexanols

*General procedure B for the cis-selective hydrogenation of phenols*

A 4 mL screw-cap glass vial, equipped with a magnetic stirring bar, was charged with [Rh(COD)Cl]₂ or [Rh–CAAC]⁶ (2-4 mol%), catalyst support (50 mg) and solid substrates (0.4 mmol, 1.0 equiv.) as indicated. Solvent (1.0 mL, 0.4 M) and liquid substrates were added. The prepared glass vial was placed in a 150 mL stainless steel autoclave under air. The autoclave was pressurized and depressurized with hydrogen gas three times before the indicated pressure was set. The reaction mixture was stirred at 40 °C for 24 h. After the autoclave was carefully depressurized, the crude mixture was purified by column chromatography on silica gel.

3a, colorless oil, procedure B: [Rh(COD)Cl]₂ 2 mol% catalyst loading, support: 4Å MS (50 mg), 5 bar H₂, solvent: n-heptane (0.4 M, 1.0 mL), temperature: 40 °C. Purification with 10% to 20% Et₂O in pentane. 77% total yield, 91:9 d.r. determined by ¹H NMR. The major diastereomer was isolated and characterized. The hydroxy group occupies the axial position based on the ³Jeq,ax coupling of HeqC₁. The J coupling of HC₄ could not be determined due to overlapping multiplets.

¹H NMR (400 MHz, CDCl₃) δ 3.94 (tt, ³JHH = 4.8 Hz, ³JHH = 3.1 Hz, 1H, HeqC₁), 1.79 – 1.65 (m, 2H), 1.62 – 1.39 (m, 6H), 1.39 – 1.23 (m, 2H), 0.91 (d, ³JHH = 6.1 Hz, 3H);
³¹C NMR (101 MHz, CDCl₃) δ 67.1, 32.4, 31.3, 29.1, 21.8;
ESI-MS calculated [C₇H₁₄O+Na]+ 137.0937, found: 137.0903.
Analytical data are in good accordance with those previously reported for this compound.¹
3ab, colorless oil, procedure A: 4 mol% catalyst loading, 10 bar H₂, solvent: n-heptane (0.4 M, 1.0 mL). Purification with 10% Et₂O in CH₂Cl₂. 86% total yield, 83:17 d.r. determined by ¹H NMR. The major diastereomer was isolated and characterized (77% yield). Procedure B: [Rh(COD)Cl]₂ 4 mol% catalyst loading, support: 4Å MS (50 mg), 5 bar H₂, solvent: n-heptane (0.4 M, 1.0 mL), temperature: 40 °C. 74% total yield, 73:27 d.r. determined by ¹H NMR. The major diastereomer was isolated and characterized (48% yield).

¹H NMR (300 MHz, CDCl₃) δ 3.57 (m, 1H, H₁), 2.00 – 1.88 (m, 2H), 1.80 – 1.70 (m, 1H), 1.69 (bs, 1H, HO), 1.59 (dm, ²JHH = 12.9 Hz, 1H), 1.51 – 1.35 (m, 1H), 1.35 – 1.18 (m, 1H), 1.17 – 1.01 (m, 1H), 0.92 (d, ³JHH = 6.6 Hz, 3H), 0.87 – 0.68 (m, 2H);

¹³C NMR (75 MHz, CDCl₃) δ 71.0, 44.8, 35.6, 34.2, 31.6, 24.3, 22.5;

ESI-MS calculated [C₇H₁₄O+Na]⁺ 137.0937, found: 137.0904.

Analytical data are in good accordance with those previously reported for this compound.

3ac, colorless oil, procedure B: [Rh(COD)Cl]₂ 2 mol% catalyst loading, support: 4Å MS (50 mg), 5 bar H₂, solvent: n-heptane (0.4 M, 1.0 mL), temperature: 40 °C. Purification with 5% to 30% EtOAc in pentane. 70% total yield, >95:5 d.r. determined by ¹H NMR. The major diastereomer was isolated and characterized (63% yield).

¹H NMR (400 MHz, CDCl₃) δ 3.77 (m, 1H, H₁), 1.79 – 1.69 (m, 1H), 1.67 – 1.57 (m, 2H), 1.56 – 1.47 (m, 2H), 1.44 – 1.31 (m, 4H), 1.30 – 1.19 (m, 1H), 0.93 (d, ³JHH = 6.9 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 71.3, 36.0, 32.7, 28.9, 24.7, 20.8, 17.1;

Analytical data are in good accordance with those previously reported for this compound.

3b, white solid, procedure B: [Rh(COD)Cl]₂ 2 mol% catalyst loading, support: SiO₂ (50 mg), 10 bar H₂, solvent: n-heptane (0.4 M, 1.0 mL), temperature: 40 °C. Purification with 5% to 20% EtOAc in pentane. 90% total yield, 93:7 d.r. determined by GC-MS. Both diastereomers were isolated and characterized together.

¹H NMR (400 MHz, CDCl₃) δ 4.03 (m, 1H, H₁), 1.87 – 1.79 (m, 2H), 1.58 – 1.42 (m, 4H), 1.37 (m, 2H), 1.24 (s, 1H), 0.99 (m, 1H), 0.86 (s, 9H);

¹³C NMR (101 MHz, CDCl₃) δ 66.1, 48.2, 33.6, 32.7, 27.6, 21.1;

IR ν = 3395, 2938, 2864, 1558, 1363, 1276, 1180, 1147, 1029, 1007, 958, 928, 904;

Analytical data are in good accordance with those previously reported for this compound.

GC-MS (prior to purification):
Rh-catalyzed (*cis*)

| peak | R.T. | first | max | last | PK | peak | corr. | corr. | % of total |
|------|------|-------|-----|------|----|------|-------|-------|------------|
| #    | min  | scan  | scan| scan | TV | height | area  | % max. |           |
| 1    | 6.359| 383   | 389 | 394 | H  | 855497| 6529607| 100.0%| 93.283%   |
| 2    | 6.416| 394   | 397 | 404 | H4| 28459 | 478131 | 7.28% | 6.717%    |

**3c**, colorless oil, procedure A: 4 mol% catalyst loading, 10 bar H₂, solvent: *n*-heptane (0.4 M, 1.0 mL). Purification with 30% Et₂O in pentane. 80% total yield, 91:9 d.r. determined by ¹H NMR. The major diastereomer was isolated and characterized (73% yield). Procedure B: 2 mol% catalyst loading, 10 bar H₂, solvent: *n*-heptane (0.4 M, 1.0 mL). Purification with 30% Et₂O in pentane. 85% total yield, 66:34 d.r. determined by ¹H NMR.

**¹H NMR** (400 MHz, CDCl₃) δ 3.56 (dm, ³Jₘₐₓₐₓ = 10.7 Hz, 1H, HₐₐC₁), 2.11 – 1.89 (m, 3H), 1.80 (dm, ²Jₜₜ = 12.6 Hz, 1H), 1.67 (dm, ²Jₜₜ = 12.3 Hz, 1H), 1.29 – 1.00 (m, 3H), 0.99 – 0.88 (m, 2H), 0.85 (s, 9H);

**¹³C NMR** (101 MHz, CDCl₃) δ 72.0, 46.8, 37.3, 35.9, 32.5, 27.7, 26.4, 24.5;

**ESI-MS** calculated [C₁₀H₂₀O⁺Na⁺] 179.1406, found: 179.1401;

**IR** ʋ = 3320, 2935, 2859, 1559, 1457, 1395, 1365, 1240, 1060, 1015, 976, 842;

Analytical data are in good accordance with those previously reported for this compound.¹

**3d**, white solid, procedure B: [Rh–CAAC] 2 mol% catalyst loading, support: SiO₂ (50 mg), 10 bar H₂, solvent: *n*-heptane (0.4 M, 1.0 mL), temperature: 40 °C. Purification with 20% to 50% EtOAc in pentane. 98% total yield, 63:37 d.r. determined by GC-MS. The major diastereomer was isolated and characterized (47% yield).

**¹H NMR** (300 MHz, CDCl₃) δ 4.53 (s, 1H), 3.88 (t, ³Jₜₜ = 3.9 Hz, 1H, HCl₁), 3.52 (s, 1H), 1.73 – 1.55 (m, 8H), 1.44 (s, 10H);
$^{13}$C NMR (75 MHz, CDCl$_3$) δ 155.4, 79.3, 66.5, 47.9, 31.4, 28.6, 27.8

**ESI-MS** calculated [C$_{11}$H$_{21}$NO$_3$+Na]$^+$ 238.1414, found: 238.1421;

**IR** $\tilde{\nu}$ = 3355, 2980, 1696, 1684, 1558, 1521, 1507, 1173, 1070, 1026, 973, 954;

Analytical data are in good accordance with those previously reported for this compound.$^9$

**GC-MS** (prior to purification):

Rh-catalyzed ($cis$)

[[$\text{Rh(COD)Cl}_2$]-catalyzed hydrogenation:]

| peak | RT  | max | last | PK | corr. | corr. | % of total |
|------|-----|-----|------|----|-------|-------|------------|
| #    | min | scan| scan | scan| area  | area  |           |
| 1    | 26.054 | 3713| 3748 | 3762 | BU    | 183342| 2837564    | 100.00%    | 62.60%    |
| 2    | 26.194 | 3762| 3772 | 3799 | UU 3  | 48674 | 1695297 | 59.74%     | 37.40%    |

Product 3d could not be observed by GC-MS or TLC. A possible pathway of decomposition is cleavage of the Boc-group and formation of the highly polar 4-aminocyclohexanol.

3e, colorless oil, 2 mol% [Rh(COD)Cl]$_2$, support: 4Å MS (50 mg), 10 bar H$_2$, solvent: n-heptane (0.4 M, 1.0 mL). Purification with 30% to 40% EtOAc in pentane. 90% total yield, 73:27 d.r. determined by

**$^1$H NMR**. The major diastereomer was isolated and characterized (64% yield).

**$^1$H NMR** (400 MHz, CDCl$_3$) δ 3.95 (pseudo-p, $^3$J$_{HH}$ = 4.7 Hz, 1H, HCl), 3.65 (s, 3H), 2.38 – 2.26 (m, 2H), 1.76 – 1.64 (m, 2H), 1.62 – 1.46 (m, 6H), 1.45 – 1.22 (m, 4H);

**$^{13}$C NMR** (101 MHz, CDCl$_3$) δ 174.6, 66.9, 51.6, 36.0, 32.3, 31.9, 31.2, 26.7;

**ESI-MS** calculated [C$_{10}$H$_{18}$O$_3$+Na]$^+$: 209.1148, found: 209.1147;

**IR** $\tilde{\nu}$ = 3372, 2924, 2855, 1736, 1437, 1258, 1202, 1159, 1072, 1034, 986, 877, 682, 644.

S44
3f, yellow oil, procedure B: [Rh–CAAC] 2 mol% catalyst loading, support:

SiO₂ (50 mg), 5 bar H₂, solvent: n-heptane (0.4 M, 1.0 mL), temperature:
40 °C. Purification with 5% to 50% EtOAc in pentane. 76% total yield, 80:20 d.r. determined by GC-MS. Both diastereomers were isolated and characterized together.

¹H NMR (400 MHz, CDCl₃) δ 3.71 (m, 1H, H₁), 3.32 (m, 3H), 3.30 – 3.11 (m, 1H), 2.06 – 1.92 (m, 1H), 1.89 – 1.77 (m, 2H), 1.70 – 1.61 (m, 4H), 1.59 – 1.49 (m, 2H), 1.42 (s, 1H), 1.37 – 1.26 (m, 1H);

¹³C NMR (101 MHz, CDCl₃) δ 78.2, 75.7, 69.8, 68.6, 56.1, 55.7, 32.7, 30.6, 29.0, 27.2;

ESI-MS calculated [C₇H₁₄O₂+Na]⁺ 153.0886, found: 153.0883;

Analytical data are in good accordance with those previously reported for this compound.

GC-MS (prior to purification):

Rh-catalyzed (cis)
[Rh(COD)Cl]$_2$-catalyzed hydrogenation:

\[
\text{MeO} \quad \text{OH} \quad \text{MeO} \quad \text{OH}
\]

$\text{H}_2$ (10 bar) [Rh(COD)Cl]$_2$ (1 mol%), SiO$_2$

$n$-heptane (0.4 M), 40 °C

3g, white solid, procedure B: [Rh–CAAC] 2 mol% catalyst loading, support: 4 Å MS (50 mg), 50 bar H$_2$, solvent: $n$-heptane (0.4 M, 1.0 mL), temperature: 40 °C. Purification with 10% to 20% EtOAc in CH$_2$Cl$_2$. 94% total yield, 76:24 d.r. determined by GC-MS. The major diastereomer was isolated and characterized (52% yield).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.71 (m, 1H, HCl), 1.78 (m, 4H), 1.54 – 1.38 (m, 4H), 1.36 (bs, 1H), 1.24 (s, 12H), 1.11 (m, 1H);

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 83.2, 69.6, 34.6, 25.0, 24.3;

$^{11}$B NMR (128 MHz, CDCl$_3$) $\delta$ 34.4 (bs);

ESI-MS calculated [C$_{12}$H$_{23}$BO$_3$Si+Na]$^+$: 249.1632, found: 249.1648;

IR $\tilde{\nu}$ = 3309, 2987, 2926, 2852, 1370, 1307, 1224, 1143, 1062, 1052, 972, 859;

Analytical data are in good accordance with those previously reported for this compound.$^{11}$

GC-MS (prior to purification):

| peak # | R.T. (min) | First scan | max. scan | last scan | PK TV | corr. height | corr. area | % max. | total |
|--------|-----------|------------|-----------|-----------|------|--------------|------------|--------|-------|
| 1      | 4.386     | 47         | 51        | 69        | H    | 6754259      | 56801634   | 94.52% | 34.49%|
| 2      | 4.538     | 73         | 77        | 112       | H    | 5469018      | 60080337   | 100.00%| 36.45%|
| 3      | 5.920     | 306        | 313       | 332       | H    | 3248350      | 47821214   | 79.56% | 29.644%|

S46
Rh-catalyzed (cis)

[Rh(COD)Cl]₂-catalyzed hydrogenation:

3h, white solid, procedure B: [Rh–CAAC] 2 mol% catalyst loading, support: 4Å MS (50 mg), 20 bar H₂, solvent: n-heptane (0.4 M, 1.0 mL), temperature: 40 °C. Purification with 10% to 30% Et₂O in pentane. 92% total yield, 78:22 d.r. determined by GC-MS. The (volatile) major diastereomer was isolated and characterized (71% yield).
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.07 (m, HCl), 1.82 – 1.71 (m, 2H), 1.60 – 1.40 (m, 6H), 1.31 (s, 1H, HO), 0.56 (m, 1H, HC4), –0.05 (s, 9H, H$_3$C7);

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 66.9 (C1), 34.2, 25.6, 21.1, –3.3 (C7);

ESI-MS calculated [C$_9$H$_{20}$O$_3$Si+Na$^+$]: 195.1176, found: 195.1180;

IR $\tilde{\nu}$ = 3308, 2918, 1453, 1273, 1244, 1086, 999, 872, 766, 745, 702, 687, 610;

GC-MS (prior to purification):

Rh-catalyzed (cis)

[Rh(COD)Cl]$_2$-catalyzed hydrogenation:

0.4 mmol

peak R.T. first max last PK peak corr. corr. % of
# min scan scan scan TV height area % max. total
1 4.554 75 80 94 H 85688 7438607 100.00% 95.223%
2 5.404 236 238 242 H 47693 372763 5.02% 4.777%
3i, off-white solid, procedure B: [Rh–CAAC] 2 mol% catalyst loading, support: 4Å MS (50 mg), 10 bar H2, solvent: iso-propanol (0.4 M, 1.0 mL), temperature: 40 °C. Boc-protection prior to isolation by addition of NEt3 (1.5 equiv.) and Boc2O (1.5 equiv.). Purification with 10% to 20% EtOAc in pentane. 98% total yield, 94:6 d.r. determined by GC-MS. The major diastereomer was isolated and characterized (88% yield). The cis-configuration was determined based on the $^3J_{\text{eq,ax}}$ coupling between $H_{\text{ax}}C1$ & $H_{\text{ax}}C2$ and $^3J_{\text{eq,ax}}$ coupling between $H_{\text{eq}}C4$ & $H_{\text{ax}}C5$. Determination of $^3J_{\text{eq,ax}}$ coupling between $H_{\text{eq}}C4$ & $H_{\text{ax}}C5$ was possible with homonuclear decoupling experiments by irradiation at $H_3C10$. The hydroxy group occupies the equatorial position, whereas the methyl group is in the axial position.

$^1$H NMR (599 MHz, CDCl3) δ 4.32 (dm, $^3J_{\text{eq,ax}} < 4.2$ Hz, 1H, $H_{\text{eq}}C4$), 4.12 – 4.05 (m, 1H, $H_{\text{eq}}C2$), 3.56 (dm, $^3J_{\text{ax,ax}} = 10.7$ Hz, 1H, $H_{\text{ax}}C1$), 2.60 (dd, $^2J_{HH} = 12.8$ Hz, $^3J_{\text{ax,ax}} = 10.7$ Hz, 1H, $H_{\text{ax}}C2$), 2.18 (bs, 1H, HO), 1.86 (dm, $^2J_{HH} = 14.0$ Hz, 1H, $H_2C6$), 1.73 – 1.64 (m, 1H, $H_2C5$), 1.58 – 1.50 (m, 2H, $H_2C5$, $H_2C6$), 1.44 (s, 9H, $H_3C9$), 1.12 (d, $^3J_{HH} = 6.9$ Hz, 3H, $H_3C10$);

$^{13}$C NMR (151 MHz, CDCl3) δ 154.9 (C7), 79.7 (C8), 67.6 (C1), 45.3 (C2), 45.1 (C4, overlapped), 28.6 (C9), 28.5 (C5), 28.4 (C6), 15.6 (C10);

ESI-MS calculated [C$_{11}$H$_{21}$NO$_3$+Na$^+$]: 238.1414, found: 238.1424;

IR $\tilde{\nu}$ = 3470, 2945, 1668, 1418, 1368, 1344, 1256, 1240, 1157, 1144, 1071, 1028, 999, 871, 768;

GC-MS (prior to purification):

Rh-catalyzed (cis)
[Rh(COD)Cl]₂-catalyzed hydrogenation:

\[
\text{H}_2 (10 \text{ bar}) \quad \text{PrOH} (0.4 \text{ M}), 40 \,^{\circ}\text{C}, 21\, \text{h} \quad 2. \text{Boc}_2\text{O} (3.0 \text{ equiv.}), \text{NEt}_3 (3.0 \text{ equiv.}), 2\, \text{h} 
\]

\[ \text{Me} \quad \text{N} \quad \text{OH} \quad \text{Boc} \]

3i, 89:11 d.r.
6. Synthesis of Cyclohexanones

General procedure C for the reduction of phenols to ketones

A 4 mL screw-cap glass vial, equipped with a magnetic stirring bar, was charged with 5 wt% Pd/Al₂O₃ (1-2 mol%) and solid substrates (0.4 mmol, 1.0 equiv.) as indicated. 1,2-dichloroethane (1.0 mL, 0.4 M) and liquid substrates were added. The prepared glass vial was placed in a 150 mL stainless steel autoclave under air. The autoclave was pressurized and depressurized with hydrogen gas three times before the indicated pressure was set. The reaction mixture was stirred at 60 °C for 24 h. After the autoclave was carefully depressurized, the crude mixture was purified by column chromatography on silica gel.

4a, colorless oil, procedure C: 1 mol% catalyst loading, 5 bar H₂. Purification with 50% CH₂Cl₂ in pentane. 81% yield.

¹H NMR (400 MHz, CDCl₃) δ 2.38 – 2.28 (m, 4H), 2.06 – 1.95 (m, 2H), 1.94 – 1.81 (m, 1H), 1.48 – 1.35 (m, 2H), 1.02 (d, ³J = 6.5 Hz, 3H);

¹³C NMR (101 MHz, CDCl₃) δ 211.3, 41.0, 34.9, 31.3, 21.2;

GC-MS (EI) 111.9 [M]+ (100);

IR ν = 2955, 2929, 1754, 1714, 1459, 1288, 1244, 1185, 1124, 1047, 1004, 895, 806, 737;

Analytical data are in good accordance with those previously reported for this compound.¹

GC-MS spectrum of the crude reaction mixture for product 4a:
4b, colorless oil, procedure C: 2 mol% catalyst loading, 5 bar H₂. Purification with 5% EtOAc in pentane. 85% yield.

\[ \text{H NMR (400 MHz, CDCl}_3 \text{)} \delta 2.33 – 2.22 (m, 2H), 2.20 – 2.08 (m, 2H), 2.08 – 1.98 (m, 1H), 1.91 – 1.82 (m, 1H), 1.73 – 1.56 (m, 2H), 1.53 – 1.38 (m, 1H), 0.97 (s, 9H);

\[ \text{C NMR (101 MHz, CDCl}_3 \text{)} \delta 213.0, 60.4, 44.4, 32.0, 30.0, 28.8, 27.8, 26.2;

ESI-MS calculated [C₁₀H₁₈O⁺Na]⁺: 177.1250, found: 177.1250.

Analytical data are in good accordance with those previously reported for this compound.¹²

GC-MS spectrum of the crude reaction mixture for product 4b:

4c, yellow oil, procedure C: 2 mol% catalyst loading, 5 bar H₂. Purification with 30% to 50% EtOAc in pentane. 50% yield.

\[ \text{H NMR (400 MHz, CDCl}_3 \text{)} \delta 4.18 (tt, J = 6.6, 3.3 Hz, 1H), 2.68 – 2.52 (m, 2H), 2.36 – 2.23 (m, 2H), 2.10 – 1.91 (m, 4H), 1.86 (bs, 1H);

\[ \text{C NMR (101 MHz, CDCl}_3 \text{)} \delta 211.1, 77.2, 66.4, 37.3, 33.9;

ESI-MS calculated [C₆H₁₀O₂⁺Na]⁺ 137.0573, found: 137.0556.

Analytical data are in good accordance with those previously reported for this compound.¹³

GC-MS spectrum of the crude reaction mixture for product 4c:
4d. white solid, procedure C: 2 mol% catalyst loading, 5 bar H₂.
Purification with 20% to 30% EtOAc in pentane. 70% yield.

\[ ^1H \text{ NMR (500 MHz, CDCl}_3 \delta 3.68 (s, 3H), 2.41 – 2.26 (m, 6H), 2.08 - 2.01 (m, 2H), 1.79 – 1.69 (m, 1H), 1.69 – 1.63 (m, 2H), 1.46 – 1.34 (m, 2H); \]

\[ ^{13}C \text{ NMR (126 MHz, CDCl}_3 \delta 211.9, 174.1, 51.8, 40.7, 35.6, 32.4, 32.0, 30.6; \]

ESI-MS calculated [C₁₀H₁₆O₃+Na]^+: 207.0992, found: 207.1009;

IR \( \tilde{\nu} = \) 2953, 2930, 1734, 1713, 1437, 1381, 1319, 1267, 1198, 1167, 1144, 980, 852, 733, 702.

GC-MS spectrum of the crude reaction mixture for product 4d:

4e, yellow oil, procedure C: 2 mol% catalyst loading, 5 bar H₂. Purification with 5% to 10% EtOAc in pentane. 73% yield.

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \delta 2.46 – 2.20 (m, 4H), 2.11 – 1.98 (m, 2H), 1.79 (m, 2H), 1.32 (t, J_{HH} = 10.2, 3.9 Hz, 1H), 1.24 (s, 12H); \]

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3 \delta 212.7, 83.5, 42.4, 28.7, 24.9; \]

\[ ^{11}B \text{ NMR (96 MHz, CDCl}_3 \delta 33.5 (bs); \]

ESI-MS calculated [C₁₂H₂₁BO₃+Na]^+: 247.1478, found: 247.1494;

IR \( \tilde{\nu} = \) 2976, 2931, 1713, 1379, 1339, 1316, 1225, 1142, 980, 966, 853, 772, 669.
GC-MS spectrum of the crude reaction mixture for product 4e:

![Graph of GC-MS spectrum]

| peak | R.T. | First | max | last | PK | peak | corr. | corr. | % of total |
|------|------|-------|-----|------|----|------|-------|-------|------------|
| #    | min  | scan | scan| scan| TV | height | area  | % max. |            |
| ---  | -----| -----|-----|-----|----|--------|-------|--------|------------|
| 1    | 7.514| 592  | 585 | 596 | M2 | 122039 | 1709327| 7.06%  | 7.299%     |
| 2    | 7.597| 596  | 599 | 606 | M  | 3135609| 21742202| 100.00%| 92.711%    |

4f, yellow oil, procedure C: 2 mol% catalyst loading, 5 bar H₂. Purification with 1% to 5% MeOH in CH₂Cl₂. 69% yield.

**1H NMR** (500 MHz, Methanol-\(d_4\)) \(\delta\) 4.05 (dd, \(J = 9.5, 5.8\) Hz, 1H), 3.33 – 3.24 (m, 2H), 2.21 – 2.13 (m, 1H), 2.00 – 1.92 (m, 1H), 1.90 – 1.80 (m, 1H), 1.80 – 1.71 (m, 1H);

**13C NMR** (126 MHz, Methanol-\(d_4\)) \(\delta\) 175.6, 68.7, 42.9, 30.5, 21.1;

**ESI-MS** calculated [C₅H₉N₂O₂+Na]⁺: 138.1212, found: 138.0511;

**IR** \(\tilde{\nu}\) = 3251, 2955, 1653, 1559, 1457, 1374, 1288, 1091, 901, 827, 750;

Analytical data are in good accordance with those previously reported for this compound.\(^{14}\)
7. Application

Acetic anhydride (85 µL, 0.9 mmol, 3.0 equiv.) was added to a solution of trans-4-tert-butylcyclohexanol (47 mg, 0.3 mmol, 1.0 equiv.) in pyridine (0.6 mL, 0.5 M) and stirred for 16 h at room temperature. After addition of water, the mixture was extracted with Et₂O (3 x 5 mL) and dried over magnesium sulfate. The crude product was purified by column chromatography on silica gel (5% Et₂O in n-pentane) to provide 5 as a colorless oil (56 mg, 0.28 mmol, 94%).

\(^1\)H NMR (300 MHz, CDCl₃) δ 4.75 – 4.48 (m, 1H), 2.08 – 1.95 (m, 4H), 1.87 – 1.73 (m, 2H), 1.37 – 1.21 (m, 3H), 1.18 – 0.96 (m, 3H), 0.84 (s, 9H);

\(^{13}\)C NMR (75 MHz, CDCl₃) δ 170.9, 73.9, 47.2, 32.5, 32.2, 27.7, 25.6, 21.6;

ESI-MS calculated [C₁₂H₂₂O₂+Na]⁺: 221.1512, found: 221.1511;

IR ν = 2946, 2864, 1735, 1468, 1452, 1367, 1240, 1046, 1027, 971, 904, 894.

4.0 M HCl in 1,4-dioxane (2.6 mL, 10.5 mmol, 10.0 equiv.) was added to a solution of trans-4-Boc-aminocyclohexanol (226 mg, 1.05 mmol, 1.0 equiv.) in 1,4-dioxane (1.3 mL, 0.8 M). The mixture was stirred for 16 h at room temperature and the solvent was evaporated. The product was obtained as a white solid (160 mg, 1.05 mmol, 99%).

\(^1\)H NMR (400 MHz, Methanol-d₄) δ 3.62 – 3.49 (m, 1H), 3.07 (t, J = 11.2 Hz, 1H), 2.03 (t, J = 10.5 Hz, 4H), 1.56 – 1.25 (m, 4H);

\(^{13}\)C NMR (101 MHz, Methanol-d₄) δ 69.5, 50.7, 33.8, 29.9;

ESI-MS calculated [C₆H₁₄NO+H]⁺: 116.1070, found: 116.1068;

IR ν = 3250, 2932, 2898, 2854, 1683, 1630, 1613, 1537, 1460, 1391, 1365, 1162, 1071, 1050, 947, 899.
The synthesis was conducted according to a modified literature procedure. A mixture of trans-4-aminocyclohexanol (115 mg, 1.0 mmol, 1.0 equiv.) and 2-amino-3,5-dibromobenzaldehyde (335 mg, 1.2 mmol, 1.0 equiv.) in ethanol (5.0 mL, 0.2 M) was heated to 90 °C for 6 h. After cooling to room temperature, NaBH₄ (91 mg, 2.4 mmol, 2.4 equiv.) was added and the mixture was stirred at room temperature for 17 h. Saturated, aqueous NH₄Cl solution was added to quench the reaction. The mixture was basified with saturated, aqueous K₂CO₃ solution and extracted with EtOAc (3 x 30 mL). The combined extracts were dried over magnesium sulfate and the crude product was purified by silica gel chromatography (5% MeOH in CH₂Cl₂). The product was dissolved in methanol and treated with 4M HCl in 1,4-dioxane. After evaporation of the solvent, Ambroxol hydrochloride 6 was obtained as a white solid (379 mg, 0.91 mmol, 91%).

¹H NMR (400 MHz, Methanol-d₄) δ 7.64 (d, J = 2.2 Hz, 1H), 7.46 (d, J = 2.2 Hz, 1H), 4.24 (s, 2H), 3.63 – 3.52 (m, 1H), 3.22 (tt, J = 11.7, 3.8 Hz, 1H), 2.24 (d, J = 12.4 Hz, 2H), 2.07 (d, J = 11.0 Hz, 2H), 1.62 – 1.47 (m, 2H), 1.43 – 1.27 (m, 2H);

¹³C NMR (101 MHz, Methanol-d₄) δ 144.8, 136.8, 134.4, 120.0, 112.0, 109.5, 69.6, 58.4, 46.2, 33.9, 28.2;

ESI-MS calculated [C₁₃H₁₉B₂N₂O+H]⁺: 376.9859, found: 378.9835;

IR v = 3192, 2919, 2914, 2853, 2699, 2685, 1630, 1584, 1458, 1413, 1286, 1062, 896, 865.
8. X-ray Diffraction Data

X-ray crystal structure analysis of 2f: A colorless plate-like specimen of C$_{11}$H$_{21}$NO$_3$, approximate dimensions 0.052 mm x 0.069 mm x 0.120 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 2140 frames were collected. The total exposure time was 24.99 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using an orthorhombic unit cell yielded a total of 33803 reflections to a maximum θ angle of 69.27° (0.82 Å resolution), of which 4551 were independent (average redundancy 7.428, completeness = 99.7%, R$_{int}$ = 7.66%, R$_{sig}$ = 4.69%) and 4145 (91.08%) were greater than 2σ(F$^2$). The final cell constants of a = 9.8601(3) Å, b = 5.6544(2) Å, c = 44.1243(15) Å, volume = 2460.06(14) Å$^3$, are based upon the refinement of the XYZ-centroids of 9942 reflections above 2σ(I) with 8.015° < θ < 138.3°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.792. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9230 and 0.9660. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group Pca$_2_1$, with Z = 8 for the formula unit, C$_{11}$H$_{21}$NO$_3$. The final anisotropic full-matrix least-squares refinement on F$^2$ with 290 variables converged at R1 = 5.72%, for the observed data and wR2 = 13.08% for all data. The goodness-of-fit was 1.094. The largest peak in the final difference electron density synthesis was 0.226 e/Å$^3$ and the largest hole was -0.215 e/Å$^3$ with an RMS deviation of 0.053 e/Å$^3$. On the basis of the final model, the calculated density was 1.163 g/cm$^3$ and F(000), 944 e$. The hydrogens at O1A, O1B, N1A and N1B atoms were refined freely, but with distance restraints (SADI, DFIX, U-fixed value). CCDC Nr.: 2004851.

![Crystal structure of compound 2f](image)

**Figure S1.** Crystal structure of compound 2f. Thermal ellipsoids are shown at 30% probability.
X-ray crystal structure analysis of 2m: A colorless plate-like specimen of C_{12}H_{16}O, approximate dimensions 0.035 mm x 0.136 mm x 0.164 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 1243 frames were collected. The total exposure time was 22.04 hours. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 10527 reflections to a maximum θ angle of 68.73° (0.83 Å resolution), of which 1794 were independent (average redundancy 5.868, completeness = 99.6%, R_{int} = 3.26%, R_{sig} = 2.44%) and 1589 (88.57%) were greater than 2σ(F^2). The final cell constants of a = 14.6389(3) Å, b = 5.30300(10) Å, c = 13.1361(3) Å, β = 106.9940(10)°, volume = 975.23(4) Å^3, are based upon the refinement of the XYZ-centroids of 5882 reflections above 20 σ(I) with 6.313° < 2θ < 137.4°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.895. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9120 and 0.9800. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P2_1/c, with Z = 4 for the formula unit, C_{12}H_{16}O. The final anisotropic full-matrix least-squares refinement on F^2 with 122 variables converged at R1 = 3.41%, for the observed data and wR2 = 8.67% for all data. The goodness-of-fit was 1.049. The largest peak in the final difference electron density synthesis was 0.197 e/Å^3 and the largest hole was -0.197 e/Å^3 with an RMS deviation of 0.032 e/Å^3. On the basis of the final model, the calculated density was 1.200 g/cm^3 and F(000), 384 e. The hydrogen at O1 atom was refined freely. CCDC Nr.: 2004853.

**Figure S2.** Crystal structure of compound 2m. Thermal ellipsoids are shown at 50% probability.
X-ray crystal structure analysis of 2o: A colorless plate-like specimen of C_{15}H_{28}O_{2}, approximate dimensions 0.056 mm x 0.148 mm x 0.152 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 601 frames were collected. The total exposure time was 8.35 hours. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 15292 reflections to a maximum θ angle of 66.87° (0.84 Å resolution), of which 2523 were independent (average redundancy 6.061, completeness = 99.1%, R_{int} = 6.24%, R_{sig} = 4.68%) and 2197 (87.08%) were greater than 2σ(F^2). The final cell constants of a = 9.1475(2) Å, b = 19.6782(5) Å, c = 7.9541(2) Å, β = 92.1100(10)^°, volume = 1430.82(6) Å³, are based upon the refinement of the XYZ-centroids of 8274 reflections above 2σ(I) with 8.987° < 2θ < 133.6°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.776. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9210 and 0.9700. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P_{2}1/c, with Z = 4 for the formula unit, C_{15}H_{28}O_{2}. The final anisotropic full‐matrix least‐squares refinement on F^2 with 165 variables converged at R1 = 7.29%, for the observed data and wR2 = 20.31% for all data. The goodness-of-fit was 1.122. The largest peak in the final difference electron density synthesis was 0.391 e/Å^3 and the largest hole was -0.403 e/Å^3 with an RMS deviation of 0.112 e/Å^3. On the basis of the final model, the calculated density was 1.116 g/cm^3 and F(000), 536 e. The hydrogens at O1 and O2 atoms were refined freely. CCDC Nr.: 2004854.

**Figure S3.** Crystal structure of compound 2o. Thermal ellipsoids are shown at 50% probability.
X-ray crystal structure analysis of **2q**: A colorless plate-like specimen of C$_{11}$H$_{21}$NO$_3$, approximate dimensions 0.075 mm x 0.079 mm x 0.158 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 2380 frames were collected. The total exposure time was 48.50 hours. The frames were integrated with the Bruker SAINT software package using a wide-frame algorithm. The integration of the data using an orthorhombic unit cell yielded a total of 65017 reflections to a maximum $\theta$ angle of 66.59° (0.84 Å resolution), of which 2113 were independent (average redundancy 30.770, completeness = 99.8%, $R_{\text{int}} = 10.21\%$, $R_{\text{sig}} = 2.93\%$) and 1684 (79.70%) were greater than 2\(\sigma(F^2)\). The final cell constants of $a = 9.2362(3)$ Å, $b = 10.9879(3)$ Å, $c = 23.7378(7)$ Å, volume = 2409.06(12) Å$^3$, are based upon the refinement of the XYZ-centroids of 9865 reflections above 20 $\sigma(I)$ with 7.448° < $\theta$ < 134.4°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.856. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.8980 and 0.9500. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $Pbca$, with $Z = 8$ for the formula unit, C$_{11}$H$_{21}$NO$_3$. The final anisotropic full-matrix least-squares refinement on F$^2$ with 141 variables converged at R$_1 = 5.90\%$, for the observed data and wR$_2 = 15.49\%$ for all data. The goodness-of-fit was 1.071. The largest peak in the final difference electron density synthesis was 0.317 e/Å$^3$ and the largest hole was -0.219 e/Å$^3$ with an RMS deviation of 0.045 e/Å$^3$. On the basis of the final model, the calculated density was 1.187 g/cm$^3$ and F(000), 944 e$. CCDC Nr.: 2004852.

**Figure S4.** Crystal structure of compound **2q**. Thermal ellipsoids are shown at 15% probability.
9. Mechanistic Studies

9.1 Deuteration Experiments

The deuteration was conducted according to general procedure A for the trans-selective hydrogenation of phenols using deuterium gas instead of hydrogen gas. The major trans-isomer was isolated by column chromatography on silica gel and analyzed by $^1$H and $^2$H NMR spectroscopy.

Scheme S1. Deuteration of $p$-tBu-phenol and 4-tBu-cyclohexanone under standard conditions for the trans-selective hydrogenation of phenols. d.r. values determined by GC-MS analysis. All experiments conducted on 0.4 mmol scale.

Deuteration of $p$-tBu-phenol revealed a syn-addition of D$_2$ at the 3- and 4-position (low deuterium incorporation at the axial position at carbon 3). Additionally, deuterium scrambling at the 2-position was observed, which can be rationalized due to the formation of keto-enol intermediates.

To test this hypothesis, we conducted the deuteration of 4-tBu-cyclohexanone under identical conditions. Scrambling of deuterium at the 2-position supports the formation of enol intermediates in the deuteration of ketones and phenols.
9.2 Reaction Profile

The hydrogenation was conducted on a 0.4 mmol scale according to general procedure A for the trans-selective hydrogenation of phenols using 1 mol% catalyst loading (8.5 mg, 0.004 mmol, 1 mol%). The stirring was stopped after the indicated time and the hydrogen gas was released after a 30 min cool-down period of the autoclave to avoid boiling of the solvent.

Figure S5. Reaction profile for the first 4 h of the hydrogenation of \( p-tBu \)-phenol. Relative ratios and d.r. values determined by GC-MS analysis.

The starting material \((p-tBu\)-phenol\) is quickly converted into the corresponding cyclohexanone and completely consumed after 120 min. With the consumption of the phenol the corresponding cyclohexanone reaches a maximum after around 90 min and is slowly consumed after 120 min (the effective concentration of cyclohexanone might be lower, since the corresponding enol form (unstable and short-lived) could not be detected by GC-MS and \(^1\text{H} \)NMR analysis). The formation of the cyclohexanols is slow within the first 60 min of the reaction. With increasing concentration of the cyclohexanone, the formation of the alcohols increases. In the beginning of the reaction, the cis-isomer is formed faster compared to the later course of the reaction (30 min/69:31 d.r. and 60 min/75:25 d.r.). This can be rationalized with
a fast, continuous all-syn-addition of hydrogen to the aromatic phenol until the phenol is consumed. After consumption of the phenol, the trans-isomer can be formed via keto-enol formation (see deuteration experiments), combined with desorption and re-adsorption to the catalyst surface. The rate of hydrogenation for cyclohexanone to cyclohexanols is relatively low.

To test which double bond (enol or olefin) is hydrogenated faster, a competition experiment was conducted. To mimic the steric influence as good as possible, a trisubstituted alkene double bond, since enols are inherently trisubstituted, within a disubstituted cyclohexane derivative, was chosen as the model substrate (Scheme S2).

![Scheme S2. Competitive hydrogenation of enol and alkene double bonds. The relative ratios were determined by 1H NMR analysis of the crude reaction mixture. [a]Regiomereric ratio of the silyl enol ether was determined by 1H NMR analysis.](image)

A 1:1 ratio of substrates A and B was submitted to hydrogenation conditions and the crude reaction mixture was analyzed by 1H NMR. Substrate B, bearing an alkene double bond, was almost completely hydrogenated after 30 min, whereas silyl enol ether A was hydrogenated with a significantly lower rate. Although the introduction of a TMS group to form a stable enol species is a manipulation of the substrate, it demonstrates, that the alkene double bond is hydrogenated at a significant higher rate.

The absence of olefins and enones as intermediates in the trans-selective hydrogenation of phenols can be explained by the fast hydrogenation of alkene double bonds under the employed conditions.
9.3 Hydrogenation of Intermediates

Enone intermediates IM-1 and IM-4 were synthesized by palladium-catalyzed dehydrogenative oxidation of 4-tert-Butyl-cyclohexanone following a literature procedure. IM-2 was synthesized by a modified Birch reduction, starting from p-tert-Butyl-anisole, and subsequent acid-catalyzed hydrolysis of the corresponding methyl enol ether. Silyl enol ether IM-3 was synthesized according to a literature procedure.

A) trans-Selective hydrogenation under standard conditions (general procedure A).

Scheme S3. Mechanistic experiments for the trans-selective hydrogenation of p-tert-Butyl-phenol derivatives. Relative ratios and d.r. values determined by GC-MS analysis. All experiments conducted on 0.4 mmol scale.
B) Hydrogenation of 4-tBu-cyclohexanone under standard conditions: decrease in \textit{trans}-selectivity \(\rightarrow\) cyclohexanone not key intermediate for high \textit{trans}-selectivity.

C) Hydrogenation of 4-tBu-cyclohexenone \textbf{IM-1} under standard conditions: very low decrease in \textit{trans}-selectivity \(\rightarrow\) enone \textbf{IM-1} (“diene”) possibly reaction intermediate in the \textit{trans}-selective hydrogenation of phenols.

D) Hydrogenation of 4-tBu-cyclohex-3-en-1-one \textbf{IM-2} under standard conditions: very low decrease in \textit{trans}-selectivity \(\rightarrow\) \textbf{IM-2} (“diene”) possibly reaction intermediate in the \textit{trans}-selective hydrogenation of phenols.

E) Hydrogenation of silyl enol ether \textbf{IM-3} under standard conditions: decrease in \textit{trans}-selectivity \(\rightarrow\) \textbf{IM-3} (“enol”) provides \textit{trans}-isomer as the major product, however the effect of the TMS group (“locked enol”) is not negligible. Unprotected hydroxy group necessary for high \textit{trans}-selectivity. Additionally, cleavage of the silyl ether was observed.

F) Hydrogenation of TBS-protected \(p\)-tBu-phenol: low reactivity of non-phenolic arenes under palladium-catalyzed standard conditions (89% remaining starting material).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme_s4.png}
\caption{Scheme S4. Mechanistic experiments for the \textit{trans}-selective hydrogenation of \(p\)-cresol derivatives. d.r. values determined by \textsuperscript{1}H NMR analysis. All experiments conducted on 0.4 mmol scale.}
\end{figure}

A) \textit{trans}-Selective hydrogenation under standard conditions (general procedure A).

B) Hydrogenation of 4-Me-cyclohexanone under standard conditions: significant decrease in \textit{trans}-selectivity \(\rightarrow\) cyclohexanone not key intermediate for high \textit{trans}-selectivity.

C) Hydrogenation of 4-Me-cyclohexenone \textbf{IM-4} under standard conditions: retention of \textit{trans}-selectivity \(\rightarrow\) enone \textbf{IM-4} (“diene”) possibly reaction intermediate in the \textit{trans}-selective hydrogenation of phenols.
Comparison of the diastereoselectivity in the direct hydrogenation of 4-tBu-cyclohexanone (67:33 d.r., Scheme S3, B) and 4-Me-cyclohexanone (55:45 d.r., Scheme S4, B) reveals, that the existing stereocenter has an influence on the desorption and re-adsorption on the surface. Sterically more demanding substituents in the 4-position favor the process of desorption and have a beneficial influence on the trans-selectivity. This trend can also be seen by comparison of the diastereoselectivity in the trans-selective hydrogenation of phenols (manuscript Scheme 2, substrates 2a-e). With increasing steric bulk in para-position, the diastereomeric ratio increases.
9.4 Isomerization Experiments

A) Hydrogenation of diastereomerically pure trans-4-tBu-cyclohexanol under standard conditions: no isomerization under reaction conditions → d.r. not driven by equilibrium.

B) Hydrogenation of diastereomerically pure cis-4-tBu-cyclohexanol under standard conditions: no isomerization under reaction conditions → d.r. not driven by equilibrium.

C) Hydrogenation of diastereomerically pure trans-4-tBu-cyclohexanol in the presence of p-iPr-phenol under standard conditions: no isomerization under reaction conditions for successful trans-selective phenol hydrogenation.

D) Hydrogenation of diastereomerically pure cis-4-tBu-cyclohexanol in the presence of p-iPr-phenol under standard conditions: no isomerization under reaction conditions for successful trans-selective phenol hydrogenation.

Scheme S5. Isomerization experiments with trans- and cis-4-tBu-cyclohexanol. d.r. values determined by GC-MS analysis. All experiments conducted on 0.4 mmol scale.
**9.5 Mechanistic Summary**

![Mechanistic Diagram](image)

**Figure S6.** Tentative schematic representation of the mechanism for the trans-selective hydrogenation of \( p \)-tBu-phenol catalyzed by Pd/Al\(_2\)O\(_3\).

\( p \)-tBu-phenol is quickly converted into the corresponding cyclohexanone (I). With consumption of the phenol the cyclohexanone concentration increases. The cyclohexanone is in equilibrium with the corresponding enol intermediate (II), shown by deuterium scrambling, chapter 9.1. With increasing concentration of the cyclohexanone, the formation of cyclohexanols starts. The direct hydrogenation of the ketone intermediate IM-b is relatively slow (chapter 9.2). The cis-cyclohexanol could be formed by slow, direct ketone hydrogenation of IM-b-cis (III) or fast, continuous phenol hydrogenation (all-syn H\(_2\)-addition). The direct formation of the trans-cyclohexanol, starting from the ketone, is disfavored because of steric interactions (IV).

Therefore, the favored reaction pathway for the formation of the trans-isomer is the hydrogenation of diene and enol intermediate IM-a, which can be formed by keto-enol tautomerism on the catalyst surface (II). IM-a-trans is formed by the desorption of IM-a-cis and re-adsorption as IM-a-trans (V). The process of desorption and re-adsorption could be facilitated via the formation of the more stable ketone intermediate IM-b (II). In addition, the process is favored with increasing steric bulk in the 4-position and by the high reaction temperatures. Finally, syn-addition of hydrogen to IM-a-trans provides the desired trans-cyclohexanol (VI).

Key to the high trans-selectivity in the hydrogenation of \( p \)-tBu-phenol (87:13 d.r.) compared to the direct hydrogenation of 4-tBu-cyclohexanone (67:33 d.r.) could be the low concentration of the cyclohexanone intermediate. The effective concentration of cyclohexanone might be even lower, since the unstable and short-lived diene and enol intermediates could not be detected with our analytical tools. The low cyclohexanone concentration disfavors the direct ketone hydrogenation, which would lead to the cis-isomer, and favors the tautomerization, as well as desorption and re-adsorption, leading to an increased trans ratio.
10. Reaction-Condition Based Sensitivity Assessment

The sensitivity assessment of general procedure A was conducted by following a modified procedure from Glorius and coworkers\textsuperscript{20} A description of the experiments included in the assessment is given in Table S9. Each reaction was prepared separately. Volume changes due to solvation of starting materials were neglected. All reactions were run in a suitable autoclave and stopped after 24 h. After the autoclave was carefully depressurized, the crude mixture was diluted with CH\textsubscript{2}Cl\textsubscript{2} (1.0 mL) and imidazole (2.5 equiv.), DMPA (0.2 equiv.) and TBSCI (2.0 equiv.) were added. The mixture was stirred at 40 °C for 16 h. Mesitylene was added as an internal standard and yield and diastereomeric ratio were determined by GC-FID analysis. The deviation from the yield of the 'standard' experiment was calculated for each experiment (Table S10). The deviation values are plotted in a radar diagram.

Standard conditions: \( n = 0.1 \text{ mmol, } c = 0.1 \text{ M, } V = 1.0 \text{ mL, } T = 80 \degree \text{C, } p(H_2) = 5 \text{ bar}. \)

Table S9. Preparation of sensitivity assessment of general procedure A.

| Number | Experiment | Preparation\textsuperscript{[a]} |
|--------|------------|-------------------------------|
| 0      | Standard   | Standard                      |
| 1      | high \(c\) | From 0.1 M (1.0 mL) to 0.2 M (0.5 mL) |
| 2      | low \(c\)  | From 0.1 M (1.0 mL) to 0.05 M (2.0 mL) |
| 3      | \(H_2O\)   | Add water (10 \(\mu\)L)       |
| 4      | low \(p(H_2)\) | From 5 bar to 3 bar               |
| 5      | high \(p(H_2)\) | From 5 bar to 7 bar              |
| 6      | low \(T\)  | From 80 °C to 60 °C             |
| 7      | high \(T\) | From 80 °C to 100 °C            |
| 8      | high \(O_2\) | No \(H_2\) fill-and-release cycle for the autoclave |
| 9      | low \(O_2\) | Setup under argon atmosphere     |
| 10     | big scale  | Big scale (2.0 mmol, 0.2 M, \(V = 10.0 \text{ mL, 2 mol\%}) |

\textsuperscript{[a]}Pd/Al\textsubscript{2}O\textsubscript{3} (4.3 mg, 0.002 mmol, 2 mol\%) was added to each reaction vessel.
Results:

**Table S10.** Results of sensitivity assessment of general procedure A.

| Number | Experiment | Yield / % | Deviation / % | d.r.[a] | Deviation / % |
|--------|------------|-----------|---------------|---------|---------------|
| 0      | Standard   | 90        | -             | 80:20   | -             |
| 1      | high c     | 90        | 1             | 79:21   | -7            |
| 2      | low c      | 31        | -66           | 84:16   | 33            |
| 3      | H₂O        | 84        | -6            | 79:21   | -4            |
| 4      | low p(H₂)  | 84        | -5            | 80:20   | -1            |
| 5      | high p(H₂) | 96        | 9             | 79:21   | -6            |
| 6      | low T      | 68        | -24           | 80:20   | -3            |
| 7      | high T     | 99        | 12            | 76:24   | -22           |
| 8      | high O₂    | 75        | -16           | 79:21   | -5            |
| 9      | low O₂     | 93        | 4             | 76:24   | -22           |
| 10     | big scale  | 99        | 12            | 77:23   | -18           |

[a]Diastereomeric ratio given as trans/cis ratio.

**Sensitivity: yield**

![Diagram representing sensitivity of yield](attachment:image.png)

yield
The influence on yield and diastereoselectivity was investigated by systematic variation of key reaction parameters. Notably, the yield of the reaction was found to be sensitive towards low concentration but tolerable of a range of hydrogen pressures, the presence of water, and variable oxygen levels. In general, the diastereoselectivity was insensitive towards any variation in the reaction conditions. However, there was a slight increase in diastereoselectivity connected with a drastic loss of yield when lowering the concentration.
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12. NMR Spectra

11.1 trans-Cyclohexanols
11.2 cis-Cyclohexanols

3a
11.3 Cyclohexanones

4a

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11.4 Application

\[ \text{Diagram of chemical structure} \]

\[ \text{Diagram of NMR spectroscopy} \]

S112
