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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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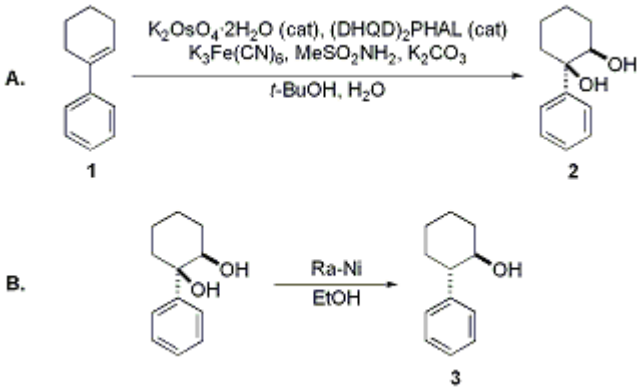
SYNTHESIS OF (+)-(1S,2R)- AND (−)-(1R,2S)-trans-2-PHENYLCYCLOHEXANOL VIA SHARPLESS ASYMMETRIC DIHYDROXYLATION (AD)

[Cyclohexanol, 2-phenyl-, (1S-trans)- and Cyclohexanol, 2-phenyl-, (1R-trans)-]



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1. Procedure

A. (+)-(1R,2R)-1-Phenylcyclohexane-cis-1,2-diol (**2**). A 3-L flask with a mechanical stirrer, thermometer and an inlet port open to the atmosphere is charged with 375 mL of water. Stirring is started and the following reagents are added in the order indicated through a powder funnel: potassium ferricyanide (247 g, 0.75 mol, 3 equiv), anhydrous potassium carbonate (104 g, 0.75 mol, 3 equiv), methanesulfonamide (23.8 g, 0.25 mol, 1 equiv), potassium osmate dihydrate (46.1 mg, 0.125 mmol, 0.05 mol %), $(DHQD)_2PHAL$ [1,4-bis(9-*O*-dihydroquinidinyl)phthalazine, 486.9 mg, 0.625 mmol, 0.25 mol %], 1-phenylcyclohexene (**1**, 39.55 g, 0.25 mol) and tert-butyl alcohol (250 mL) (Notes 1 and 2). The slurry is stirred vigorously for 2 days at a rate of 500 rpm. During this time, the product crystallizes in the top organic phase, beginning after 4 hr. Also, the appearance of the slurry gradually changes from a mixture containing red granules (ferricyanide) to yellow flakes, which are presumably a salt of iron (II).

After the reaction is complete the mixture is treated with ethyl acetate (250 mL) with stirring to dissolve the product. The resulting mixture is filtered through a 500-mL medium-fritted glass funnel and the flask and filter cake are washed with ethyl acetate (3 × 50 mL). The filtrate is transferred to a 2-L separatory funnel and the brown-colored aqueous phase is separated. The organic phase is washed with 2 M potassium hydroxide (KOH, 2 × 50 mL) with vigorous shaking to remove methanesulfonamide , then dried over magnesium sulfate ($MgSO_4$, 12.5 g). The solid is filtered, the cake is washed with ethyl acetate (2 × 37 mL) and the filtrate is evaporated, to afford a white solid. After the crude product is dried under reduced pressure overnight, it weighs 47.44 g (99%) (Notes 3 and 4).

B. (−)-(1R,2S)-trans-2-Phenyl-1-cyclohexanol (**3**). A 1-L, three-necked flask is set up with a mechanical stirrer, thermometer, reflux condenser and nitrogen line. The flask is placed in a silicone oil bath (230 × 100-mm Schott crystallizing dish). The flask is charged with a slurry containing activated W-2 Raney nickel (257.5 g) in wet ethanol (70% v/v) through a powder funnel under a blanket of nitrogen. *Caution-Fire Hazard! Raney nickel is extremely pyrophoric when dry and must be kept submerged under liquid at all times* (Note 5). This is done by transferring an aqueous slurry of Raney nickel to the flask with the aid of 250 mL of anhydrous ethanol in portions, making sure that the catalyst does not dry. The crude diol from the previous step is added to the flask, using another 50 mL of anhydrous ethanol to complete the transfer. The mixture is stirred vigorously and refluxed for 2 hr (Note

6).

The reaction mixture is allowed to cool to 40-50°C and filtered through a 1/2"-layer of Celite in a 500-mL fritted (medium) glass funnel, making sure that the liquid level does not fall below the surface of the filter cake. A total of 300 mL of ethanol in small portions is used to transfer the slurry quantitatively to the funnel and to wash the filter cake. A 170-mm × 90-mm crystallizing dish is useful to cover the top of funnel during the filtration; however it is not necessary. The Raney nickel sludge is transferred with water to a waste container.

The filtrate is concentrated under reduced pressure to remove most of the ethanol and the resulting two-phase mixture is diluted with 50 mL of saturated brine and extracted with ethyl acetate (2 × 50 mL). The organic phase is dried over $MgSO_4$ (3.75 g), filtered and evaporated under reduced pressure overnight to give the crude alcohol (35.53 g, 94.0% ee). The solid residue is crystallized from 75 mL of warm petroleum ether (bp 30-60°C). The crystallization is allowed to proceed for 3 hr at room temperature and 1 hr at 0°C. The crystalline mass is triturated with 25 mL of cold (0°C) pentane to break up the lumps. The slurry is filtered, washed with chilled pentane in portions (3 × 12.5 mL) and the solid is dried under reduced pressure overnight to constant weight, to afford 25.12 g (58% from **1**) of colorless crystals, mp 64-65°C. The enantiomeric purity was found to be >99.5% ee by chiral stationary phase SFC (supercritical-fluid chromatography) (Notes 7-8).

2. Notes

1. The potassium ferricyanide was Spectrum technical grade . Methanesulfonamide (97%), $(DHQ)_2PHAL$ (95%), potassium osmate dihydrate and tert-butyl alcohol (99.3%) were obtained from Aldrich Chemical Company, Inc. 1-Phenylcyclohexene (98%) was obtained from Acros Organics .
2. The temperature did not rise more than a few degrees above room temperature after all the reagents were added.
3. This material, which is contaminated with the chiral ligand, is sufficiently pure to be used in the next step. A small portion of the crude diol (479 mg) was purified by column chromatography (SiO_2, 30 × 160 mm, 4/1 hexane/ ethyl acetate) to yield a white solid (430 mg, 90%). The enantiomeric purity of the crude product was determined to be 99.4% ee by SFC analysis on a chiral stationary phase using a Berger Supercritical Fluid Chromatograph (Berger Instruments, Newark, DE). The diols were separated using an (R,R) Whelk-O, 250 mm × 4.6 mm, 5µ, 100 Å column at 40°C. Methanol was used as the modifier and held isocratically at 15% in CO_2. The eluent flow rate was maintained at 2.0 mL/min and the outlet pressure was isobaric at 150 bar (112,500mm, 11.3×10^4mm). All samples were prepared in methanol at concentrations of 1 mg/mL. The retention time for the diol peaks were 3.55 min for the (+)-isomer (**2**) and 3.05 min for the (−)-isomer. The enantiomeric purity of the crude product was also analyzed by HPLC using an (*R.R*) Whelk-O, 250 mm × 4.6 mm, 5µ, 100 Å column at 150 bar (112, 500mm). Isopropyl alcohol was used as the modifier and held isocratically at 15% in hexane . The eluent flow rate was maintained at 1.3 mL/min, and the retention time for the diol peaks were 7.56 min for the (+)-isomer (**2**) and 5.30 min for the (−)-isomer.
The (−)-enantiomer was prepared using this procedure with $(DHQ)_2PHAL$ as the chiral ligand. The yield of the crude diol, (−)-(1*S*,2*S*)-1-phenylcyclohexane-cis-1,2-diol , was 47.39 g (99%). The enantiomeric purity of this material was found to be 98.9% ee by CSP-SFC (see Note 4 for data). These levels of asymmetric induction are similar to those reported by Sharpless and co-workers, i.e., 99% ee for the (*R*,*R*)-isomer using AD-mix-β [containing $(DHQD)_2PHAL$] and 97% ee for the (*S*,*S*)-isomer using AD-mix-α [containing $(DHQ)_2PHAL$].[2]
4. The diol was further purified by recrystallization from ethyl acetate and petroleum ether in 62% recovery. The (+)-(1*R*,2*R*)-1-phenylcyclohexane-cis-1,2-diol thus obtained had a mp of 122-123°C (lit. mp 121-122°C)[3] and was found to have an optical purity of >99.5% ee by chiral SFC. The following physical data was observed:
(+)-(1R,2R)-1-Phenylcyclohexane-1,2-diol. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.36-1.45 (m, 1 H), 1.52-1.56 (m, 1 H), 1.65-1.75 (m, 4 H), 1.83-1.90 (m, 3 H), 2.69 (d, 1 H, J = 2.0), 3.95 (dt, 1 H, J = 4.0, 11.0), 7.27 (t, 1 H, J = 7.5), 7.38 (t, 2 H, J = 7.5), 7.50 (d, 2 H, J = 8.5) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.27, 24.58, 29.40, 38.73, 74.74, 76.01, 125.40, 127.24, 128.67, 146.67 ; IR (KBr)cm^{-1}: 3480, 3241, 3083, 3056, 3021, 2948, 2859, 1945, 1866, 1797, 1741, 1598, 1494, 1444, 1411, 1375, 1268, 1203,

1141, 1079, 1064, 991, 968, 754, 694 ; LRMS EI (relative intensity) 192 (53), 174 (13), 145 (8), 133 (100), 120 (40), 105 (56), 91 (16), 77 (31), 70 (14), 55 (23) ; $[\alpha]_D$ +16.8° (benzene, *c* 1.0) Calcd. for $C_{12}H_{16}O_2$: C; 74.97, H; 8.39. Found: C; 74.90, H; 8.62.

(−)-(1S,2S)-1-Phenylcyclohexane-1,2-diol. mp 122-123°C; $[\alpha]_D$ −16.0° (benzene, *c* 1.0); Calcd. for $C_{12}H_{16}O_2$: C; 74.97, H; 8.39. Found: C; 74.89, H; 8.62.

5. The Raney nickel (WR Grace Grade 28) was obtained as a 50 wt% aqueous slurry from Strem Chemicals Inc. The mass of the Raney nickel was determined by the following procedure:[4] The weight, in grams, of a 500-mL volumetric flask filled with deionized water was recorded (Mass A). A portion of the water was removed and replaced with the Raney Nickel slurry. The remaining volume was filled with deionized water and reweighed (Mass B). The amount of Raney nickel , in grams, was calculated using the equation Amt. = 1.167(Mass B − Mass A), where 1.167 accounts for the volume of water displaced by the Raney nickel catalyst with an average density of 7.00 g/mL. However, prior to transferring to the flask, the excess water was decanted from the material. Small spills of Raney nickel slurry were transferred with a wet Kimwipe to a waste container containing water. The ethanol was undenatured.

6. The progress of the reaction may be followed by TLC using 1:3 ethyl acetate/petroleum ether and visualization with anisaldehyde stain. The diol appears at an R_f = ≈0.3 (stains olive-brown); the 2-phenylcyclohexanol appears at an R_f = ≈0.6 (stains blue). The checkers found that the use of a needle outlet at the top of the condenser helped to maintain a smooth reflux and prevented leakage though the stirring assembly.

7. The enantiomeric purity was determined by CSP-SFC (Note 3). Samples were run isocratically at 1% methanol-modified CO_2 and the flow rate was held constant at 4.2 mL/min. Outlet pressure was isobaric at 150 bar (112,500mm, 11.3 × 10^4mm). All samples were prepared in methanol at concentrations of 1 mg/mL . The retention times for the enantiomers were 4.50 min for the (−)-isomer and 3.91 min for the (+)-isomer. The enantiomeric purity of the alcohol was also analyzed by HPLC using an (*R.R*) Whelk-O, 250 mm × 4.6 mm, 5µ, 100 Å column. Isopropyl alcohol was used as the modifier and held isocratically at 2% in hexane . The eluent flow rate was maintained at 1.3 mL/min, and the retention times for the diol peaks were 14.05 min for the (−)-isomer (**3**) and 11.46 min for the (+)-isomer.

Sublimation of a small portion of the alcohol (501 mg) at 45°C (0.05 mm) provided a white powder (467 mg, 93%), which was found to be analytically pure. The following physical data were observed:

(−)-(1*R*,2*S*)-2-phenyl-1-cyclohexanol. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.31-1.57 (m, 4 H), 1.64 (d, 1 H, *J* = 2.5), 1.78-1.80 (m, 1 H), 1.86-1.89 (m, 2 H), 2.12-2.14 (m, 1 H), 2.42-2.47 (m, 1 H), 3.64-3.69 (m, 1 H), 7.24-7.28 (m, 3 H), 7.35 (t, 3 H, *J* = 7.5) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.28, 26.27, 33.53, 34.64, 53.43, 74.63, 127.07, 128.18, 129.01, 143.57 ; IR (KBr) cm^{-1}: 3295, 3081, 3058, 3025, 2854, 2653, 1945, 1878, 1801, 1756, 1600, 1492, 1446, 1348, 1060, 964, 1130, 746, 696 ; LRMS EI (relative intensity) 176.1 (61), 158.1 (9), 143.1 (11), 130.1 (47), 117.1 (39), 104.1 (43), 91.0 (100), 85.1 (7), 77.0 (16), 71.0 (7), 65.0 (10), 57.0 (17) ; $[\alpha]_D$ −58.3° (MeOH, *c* 1.0); Calcd. for $C_{12}H_{16}O$: C; 81.77, H; 9.15. Found: C; 81.96, H; 9.28.

(+)-(1*S*,2*R*)-2-phenyl-1-cyclohexanol. mp 64-66°C; $[\alpha]_D$ +59.4° (MeOH, *c* 1.0); Calcd. for $C_{12}H_{16}O$: C; 81.77, H; 9.15. Found: C; 81.89, H; 9.23

A second batch of product was obtained by concentration and recrystallization of the mother liquor to provide another 1.89 g (4.4%) of (−)-(1*R*,2*S*)-trans-2-phenyl-1-cyclohexanol of a slightly lower enantiomeric purity (98.6% ee).

8. The other enantiomer, (+)-(1*S*,2*R*)-trans-2-phenylcyclohexanol , was also prepared by this procedure. The crude mass of the alcohol was 39.15 g (95.8% ee), while after recrystallization, the yield was 29.80 g (69%) of material with the following properties: mp 64-66°C, >99.5% ee (see Note 7 for data). The reaction appears to be scaleable since the submitters reported obtaining a 69% overall yield (122 g) of the (−) isomer from 1 when this procedure was carried out on a 1-mol scale.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Enantiomerically pure trans-2-phenylcyclohexanol, first used by Whitesell as a chiral auxiliary[5] has become a popular reagent in a number of asymmetric transformations.[6] Some recent applications include asymmetric azo-ene reactions,[7] [4 + 2]-cycloaddition reactions,[8] ketene-olefin [2 + 2]-reactions,[9] enolate-imine cyclocondensations,[10] Pauson-Khand reactions,[11] palladium annulations[12] and Reformatsky reactions.[13] Despite its potential, use of this chiral auxiliary on a preparative scale is currently limited by its prohibitive cost.

A previous *Organic Synthesis* procedure employing Whitesell's method affords both enantiomers of trans-2-phenylcyclohexanol in 3-4 steps from cyclohexene oxide via a lipase-catalyzed hydrolysis of the corresponding racemic chloroacetate ester.[14] A related reaction, the Lipase PS30-catalyzed kinetic acetylation of the racemic alcohol afforded the enantiomers in excellent yield and optical purity.[15] However, a limitation of both of these procedures is that to obtain one of the enantiomers, they require chromatographic purification of an intermediate, making scale-up impractical. The (+)-enantiomer (≥ 97% ee) has been prepared from 1-phenyl-1-cyclohexene by hydroboration with $IpcBH_2$, monoisopinocamphenylborane, but the reaction is slow, resulting in 70% conversion after 7 days at 0° C.[16] A procedure involving ring opening of cyclohexene oxide with phenyllithium in the presence of a chiral additive has been reported, but the level of asymmetric induction is modest (47% ee).[17] Other methods that have been used recently to prepare this chiral auxiliary involve enantioselective epoxidation[18] and protonation.[19]

The preparation described here is a slight modification of a route published by King and Sharpless[3] via the osmium-catalyzed asymmetric dihydroxylation (AD) reaction of 1-phenyl-1-cyclohexene.[2] The major strengths of this process are that either enantiomer can be prepared in high optical purity (> 99.5% ee) without the need for chromatography.

Some experimentation afforded improvements to the process. For example, in the case of the AD reaction, both the osmium and chiral concentrations could be reduced to a level of 0.05 mol % and 0.25 mol %, respectively, or one-fourth the levels in the commercial AD-mix formulation, without compromising the yield and enantiomeric excess of the crude product. The volume of liquid was also reduced to one-fourth of the quantities reported (1.5 L of water and 1 L tert-butyl alcohol per mole of substrate versus 5 L of water and 5 L of tert-butyl alcohol per mole of substrate). Under these conditions the reaction mixture is a slurry, but the potassium ferricyanide dissolves as it reacts. Reducing the catalyst concentration had the effect of doubling the reaction time from 1 day to 2 days. Interestingly, a study on the use of reduced amounts of osmium in the AD reaction of 1-phenyl-1-cyclohexene concluded that reducing the quantity of osmium by half (to 0.1 mol %), doubled the reaction time without affecting the yield, but that further reductions in osmium content made the reaction too sluggish to be useful.[20]

In scaling up this procedure, the biggest improvement in the overall yield was achieved by omitting the crystallization of the intermediate diol. The trans-2-phenylcyclohexanol, which forms relatively large crystals, is easier to handle than the diol, which is a very fluffy powder. Analysis of the final product was carried out by both CSP-HPLC and CSP-SFC methods.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(+)-(1S,2R)-trans-2-Phenylcyclohexanol:
Cyclohexanol, 2-phenyl-, (1S-trans)- (9); (34281-92-0)

(−)-(1R,2S)-trans-2-Phenylcyclohexanol:
Cyclohexanol, 2-phenyl-, (1R-trans)- (11); (98919-68-7)

(+)-(1R,2R)-1-Phenylcyclohexane-cis-1,2-diol:
1,2-Cyclohexanediol, 1-phenyl-, (1R-cis)- (12); (125132-75-4)

Potassium ferricyanide:
Ferrate (3−), hexacyano-, tripotassium (8);
Ferrate (3−), hexakis(cyano-C)-, tripotassium, (OC-6-11)- (9); (13746-66-2)

Methanesulfonamide (8, 9); (3144-09-0)

Potassium osmate (VI) dihydrate:
Osmic acid, dipotassium salt (8, 9); (19718-36-3)

$(DHQ)_2PHAL$: ALDRICH: Hydroquinine, 1,4-phthalazinediyl diether:
Cinchonan, 9,9"-[1,4-phthalazinediylbis(oxy)bis[10,11-dihydro-6'-methoxy-, (8α,9R)-(8"α,9"R)- (13); (140924-50-1)

1-Phenylcyclohexene:
Benzene, 1-cyclohexen-1-yl- (8, 9); (771-98-2)

tert-Butyl alcohol (8);
2-Propanol, 2-methyl- (9); (75-65-0)

Raney nickel: CANCER SUSPECT AGENT:

Nickel (8, 9); (7440-02-0)

(−)-(1S,2S)-1-Phenylcyclohexane-cis-1,2-diol:
1,2-Cyclohexanediol, 1-phenyl-, (1S-cis)- (9); (34281-90-8)

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